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Drinking Water Criteria Document for 1,1,1-Trichloroethane (Draft)

Life Systems, Inc., Cleveland, OH

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The Office of Drinking Water (ODW), U.S. Environmental Protection Agency has prepared a Drinking Water Criteria Document on 1,1,1-trichloroethane This Criteria Document is an extensive review of the following topics:

- Physical and chemical properties of 1,1,1-trichloroethane
- Toxicokinetics and human exposure to 1,1,1-trichloroethane
- Health Effects of 1,1,1-trichloroethane in humans and animals
- Mechanisms of toxicity of 1,1,1-trichloroethane
- Quantification of toxicological effects of 1,1,1-trichloroethane

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HEALTH EFFECTS BRANCH
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*Prepared by the Science and Technology Branch

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PREFACE

The objective of this document is to assess the health effect information of the contaminant 1,1,1-Trichloroethane in drinking water and to quantify toxicological effects. To achieve this objective, data on pharmacokinetics, assessment of human exposure, acute and chronic health effects in animals, human health effects including epidemiology and mechanisms of toxicity were evaluated. Only the reports which were considered pertinent for the derivation of the maximum contaminant level are cited in the document. Particular attention was paid toward the utilization of primary references for the assessment of health effects. Secondary references were used rarely. For comparison, standards and criteria developed by other organizations are discussed in Section VIII, Quantification of Toxicological Effects.

I. SUMMARY

In 1978, the estimated production of methyl chloroform in the U.S. amounted to 623 million pounds. Methyl chloroform is used extensively for industrial metal cleaning, and in the manufacturing of adhesives and various aerosol products. All of these quantities, whether used industrially or for consumer products are eventually transmitted into the environment, primarily in the form of atmospheric emissions.

The atmospheric level of methyl chloroform has been generally measured in the low parts per billion (ppb) or parts per trillion (ppt) range. Methyl chloroform undergoes a slow photochemical decomposition in the troposphere to produce carbon monoxide, hydrogen chloride, phosgene, and various other halogenated products.

Methyl chloroform has been detected in the drinking water of several cities throughout the United States. It may be of interest to note that near manufacturing sites, methyl chloroform has been detected also in surface and ground water.

Inhalation is the major route of exposure in humans, followed by food and water consumption, and dermal contact. Methyl chloroform, in its unmetabolized form, is rapidly excreted in the breath after exposure. For example, within the first hour after human inhalation of a single breath of methyl chloroform, 44% of the dose was excreted on the breath unchanged. Rats treated with an injected dose or inhalation dose excreted 98.7% on the breath in an unchanged form. Metabolism studies conducted on methyl chloroform indicated the fate of the compound in rats, mice, and man is relatively similar. The initial step in the biotransformation of methyl chloroform is the formation of the metabolic trichloroethanol which subsequently is excreted from the body as trichloroacetic acid or as trichloroethanol glucuronide.

Inhalation (exposure) estimations have been made for occupational exposure concentrations of methyl chloroform in the air surrounding various industries ranging widely from 1.5-16.6 in the metal industry to 12.0-118.0 ppm in soldering degreasing plants. Concentrations which have been reported to cause transient, mild eye irritations have been in the range of 500-1000 ppm range. Regression analysis has indicated a linear relationship between vapor concentrations of methyl chloroform and the levels of urinary metabolites.

The odor threshold of methyl chloroform covers a wide range (16 - 700 ppm) suggesting that individual sensitivity may play a part in determining resultant irritation and sensivity of various organs. The American Conference of Governmental Industrial Hygienists has recommended a Threshold Limit Value of 350 ppm.

Methyl chloroform has been found in small amounts as a contaminant in various food stuffs. Amounts of this compound in meat, oils, fats, tea, fruits, and vegetables ranged from 1 to 10 ug/kg. These levels are reportedly higher than the concentrations found in drinking water of U.S. cities.

The predominant health effects of exposure to anesthetic levels of methyl chloroform is the narcotic effect on the central nervous system (CNS). Man is the most responsive species in demonstrating such CNS effects of methyl chloroform. Most studies showed behavioral or narcotic changes on experimental animals at much higher levels of exposure than those reported for man. The effects of methyl chloroform in the CNS are similar to a general anesthetic agent; these are functional changes which, according to available reports, are entirely reversible. Inhalation of high concentrations of methyl chloroform for extended time periods could be fatal without any occurrence of organic or toxicological symptoms. Nausea and prolonged restlessness have been observed as side effects in humans receiving anesthetic doses, but consciousness returns within minutes after breathing air free of the compound.

The Romberg test (a neurological test which measures proprioceptive control) has been used to measure the narcotic effects of methyl chloroform within the range of 500 ppm (no CNS effects) to 2,650 ppm. Impairment of motor control has been demonstrated in humans with concentrations as low as 350 ppm.

However, this finding was not collaborated by other investigators.

It is generally believed that high concentrations of the chlorinated hydrocarbons can sensitize the heart of some individuals and thereby make the heart abnormally responsive to epinephrine. One of the effects of epinephrine in man and animals is cardiotoxicity. Since methyl chloroform either has arrthymic effects of its own or makes epinephrine effects more pronounced, there is a potential for serious cardiac effects resulting from exposure during excitement or stress when the body normally releases high levels of epinephrine. If an additional factor of an old cardiac scar or other cardiovascular problem is added, there is a physiological potential for serious cardiac effect from high levels of exposure.

The subcutaneous absorption of methyl chloroform appears to be dependent on the area of exposure. The rate of absorption during exposure may affect its toxic potential.

Biochemical effects on the liver also occur with methyl chloroform exposure. The liver changes occurring in man and experimental animals after exposure are not secondary to either CNS or cardiac effects of this solvent. However, these changes consist of actual cellular or biochemical damage while the CNS effects like those of most anesthetic agents are reversible.

Human liver effects have been assessed in some reports by measuring urinary urobilinogen (a bile pigment processed by liver cells and released only in small amounts by a healthy liver). Serum is frequently analyzed for enzymes (SGPT and SGOT) which increase in liver disease. The exposure level resulting in liver change has been delineated in humans and experimental animals. Animal toxicity data have shown that the guinea pig is the most sensitive species to the liver effects of methyl chloroform. Fatty changes in rodent livers were reported after chronic exposure at 1,000 ppm in four studies. However, animal experiments investigating the influence of methyl chloroform on liver function yield controversial results highly dependent on species, dose and treatment schedule. Results vary from no organic damage in guinea pigs at 1,500 ppm at 7 hr/day for 3 months to actual damage at the 1,000 ppm for 30-90 min/day exposure for 3 months.

Repeated exposure to methyl chloroform has been shown to increase the excretion of metabolites in both animals and man, probably by the mechanism of enzyme induction. The importance of this induction is twofold. First, it is a mechanism by which man and animal excrete methyl chloroform more rapidly on chronic exposure; because of this apparent capability, fewer chronic effects would be expected to occur with methyl chloroform compared with compounds that deposit in tissues. Second, stimulation or induction of some of these liver enzymes changes the action of many presecription and non-prescription drugs since the same enzymes that are induced by methyl chloroform are responsible for the metabolism of many types of drugs (i.e., sedative hypnotics and antipsychotics). Thus, some drugs may have reduced or increased effects in persons chronically exposed to methyl chloroform.

Nephrotoxicity, as measured by tubular damage, phenosulfonpthalein, glucose, and protein excretion data has been investigated in animals and man with reference to methyl chloroform. Although some kidney damage has been reported in laboratory animals, it appears that methyl chloroform damages the liver before it affects the kidneys.

The National Cancer Institute (NCI) conducted carcinogenesis bioassays on methyl chloroform. Rats and mice were orally dosed with methyl chloroform five times per week for 78 weeks. Rats received either 1,500 or 750 mg/kg of the compound; mice (male and female) received either 5,615 or 2,807 mg/kg. The dose levels administered in both experiments were sufficiently high to result in early death within each group; a maximum of 40% of the initial groups remained alive by end of dosing. Within the survival groups, no consistent pattern of cancerous tumors was observed. Due to the low survival rate, statistical analysis could not be performed in either study.

The CAG has calculated an upper-limit cancer risk estimate based on the 1983 NTP bioassay. This study showed a marginally statistically significant increase in hepatocellula carcinomas in femal mice receiving 1500 or 3000 mg/kg methyl chloroform by gavage in corn oil five times per week for 103 weeks. The responses were 6.1%, 10.2%, and 20.4% for the control, low-dose, and high dose groups, respectively. They stated that consuming 2 liters of water per day over a lifetime at a methyl chloroform concentration of 2200 ug/L, 220ug/L or 22 ug/1 would increase the risk of one excess cancer per 10,000 (10^{-4}), 100,000 (10^{-5}), or 1,000,000 (10^{-6}) people exposed, respectively.

Chronic Animal Studies

Although a number of studies have indicated changes in the heart, nervous reflex activity, respiratory function, and hepatic changes resulting from "long-term" exposure to methyl chloroform, most of these studies have used continuous exposures, which are not typical of the ingestion through water. Therefore, studies investigating the chronic effects of long-term exposure to methyl chloroform should be conducted that utilize exposure schedules to those encountered through water.

Mutagenicity, Teratogenicity, Carcinogenicity.

Mutagenic properties of methyl chloroform have been investigated yielding weakly positive responses in certain Ames tests to negative responses in some other test systems. There are three studies on the teratogenic and fetal toxicity of methyl chloroform, two of which were via inhalation and one by ingestion. The results of these suggested that methyl chloroform was not teratogenic to mice or rats at given levels of exposure.

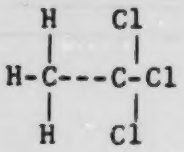
In the repeat NTP bioassay in rats and mice (draft report, 1983) there was an increase in hepatocellular carcinomas occurrence in low and high dose males and high dose females. NCl concluded that (1) methyl chloroform was not carcinogenic for male rats (2) the study was considered inadequate for carcinogenesis evaluation in female rats, (3) the association between the administration of methyl chlorofrom and the increased incidences of hepatocellular carcinomas in male mice was considered equivocal, and (4) methyl chloroform was carcinogenic for feamle mice, causing an increased incidence of hepatocellular carcinomas.

Synergistic Effects

Ingestion of excessive dose of ethanol was shown to increase the hepatotoxicity of methyl chloroform. However, from a review of the literature, it is evident that research must be intitated to answer important questions concerned with exposure to methyl chloroform and that a concerted effort must be directed toward determining the possible additive, synergistic or inhibitory effects of methyl chloroform, in combination with other hydrocarbons and organic solvents, on dose-response relationships.

II. CHEMICAL AND PHYSICAL PROPERTIES

1,1,1-Trichloroethane (CH_3CCl_3), also called methyl chloroform, is a colorless nonflammable liquid which has a characteristic odor. Its line formula is:



$$\begin{array}{ccccc} & \mathrm{H} & & \mathrm{Cl} & \\ & | & & | & \\ \mathrm{H}- & \mathrm{C} & --- & \mathrm{C} & -\mathrm{Cl} \\ & | & & | & \\ & \mathrm{H} & & \mathrm{Cl} & \end{array}$$

Table II-1 shows some of its important chemical and physical properties.

In the atmosphere, methyl chloroform is subject to free radical attack and reaction with hydroxyl radicals is the principal way in which it is scavenged from the atmosphere. Photo-oxidation products of methyl chloroform include hydrogen chloride, carbon oxides, phosgene, and acetyl chloride (Christiansen et al. 1972). The principal tropospheric photo-oxidation product has been reported to be trichloroacetal-dehyde.

In water, methyl chloroform is slowly hydrolyzed to predominantly acetic and hydrochloric acids (Dilling et al. 1975). Dilling et al. (1975) reported a half-life of hydrolysis of 6 months at 25°C.

Table II-1. Physical Properties of Methyl Chloroform

Solubility in water @ 25°C	0.44 gm/100 gm
Boiling point @ 760 torr	74°C
Vapor pressure @ 20°C	100 torr
Vapor density (air = 1)	4.6
Molecular weight	133.41

Anhydrous methyl chloroform is generally noncorrosive, but in the presence of water it can react to form hydrochloric acid, which is a corrosive of metals (Keil 1979). Addition of epoxides can neutralize the generated acid (Keil 1979). Anhydrous methyl chloroform when heated to 360° to 440°C, decomposes to 1,1-dichloroethylene and hydrogen chloride. When methyl chloroform is heated in the presence of water at temperatures between 75° and 160°C, it decomposes upon contact with metallic chlorides or sulfuric acid to acetyl chloride, acetic acid, and acetic anhydride. Noweir et al. (1972) have observed that when methyl chloroform comes in contact with iron, copper, zinc, or aluminum, at elevated temperatures, phosgene is produced.

III. METABOLISM AND PHARMACODYNAMIC EFFECTS

A. Metabolism

1. Absorption

In assessing the relationship of absorption of methyl chloroform, one needs to consider the types of action involved in the chlorinated hydrocarbons. They are all neurodepressants and they are all affected by the rate of absorption during exposure by inhalation, the most common route of exposure in man.

Differences in the rate of absorption, as reflected in the partition coefficients, could account for the approximately ten-fold greater toxicity of the 1,1,2-isomer over the toxicity of methyl chloroform (Fairchild et al. 1977). The blood/air partition coefficients are 1.4 for methyl chloroform and 44.2 for 1,1,2-trichloroethane (Morgan et al. 1972). The body content of the latter will increase much more rapidly than the former during exposure to equal concentrations of vapor. Following exposure, the body content of methyl chloroform will decrease much more rapidly by excretion in breath than that of its 1,1,2-isomer, leaving less in the body to be metabolized.

According to Stewart and Dodd (1964), cutaneous absorption depends on the area of exposure. Methyl chloroform is more readily absorbed through the skin than is trichloroethylene. Because continuous immersion of both hands in methyl chloroform for 30 minutes has been estimated to be equivalent to a 30-minute vapor exposure to 100-500 ppm of the compound, skin absorption would present only a limited health hazard. In Stewart and Dodd's experiments, both male and female subjects ranging in age from 25 to 62 years were used. Three kinds of hand exposure were tested: thumb immersion; total hand immersion; and topical hand application, which consisted of brief immersion, withdrawal, solvent evaporation, and reimmersion. Alveolar air samples were measured during and following exposure. Methyl chloroform in the alveolar air increased rapidly during immersion and dropped off slowly following exposure. The results are shown in Table III-1. Considerable effort was taken that the exposure through the skin was not confounded by vapor inhalation. Periodically, during the skin exposure, samples of breathing zone air were analyzed. Inhalation, as a source of the methyl chloroform in this experiment, was not a factor (Stewart and Dodd 1964). Male and female human subjects ranging in age from 25 years to 62 years were used. Three types of exposures were tested: thumb immersion, hand immersion, and topical application on the hand.

Table III-1 Absorption of Methyl Chloroform

Length of exposure (min)	Type of exposure	ppm Average Peak breath concentration	ppm Average breath concentration 2 hour post-exposure
30	Thumb (immersion)	1.0	0.31
30	Hand (immersion)	21.5	1.55
30	Hand (topical)	0.65	0.31

Adapted from Stewart and Dodd (1964).

The experiment was carefully designed to prevent the subjects from inhaling the chemical. The authors concluded that cutaneous absorption presents no health hazard since immersion of both hands for 30 minutes is equivalent to a 30-minute vapor exposure to 100-500 ppm of the chemical.

Fukabori et al. (1976) studied the percutaneous absorption of methyl chloroform applied on 12.5 cm^2 of the skin of the forearm. Four men ranging from 24 years to 51 years of age were used. Application of the chemical for two hours a day on five consecutive days resulted in a maximum concentration of 7 ppm in the expired air and 9 mg/ml in the blood immediately after termination of the daily application. Comparable results were obtained when both hands were immersed in the test compound 11 times a day for 10 minutes on four consecutive days. The concentration of methyl chloroform obtained in the alveolar air in these experiments was comparable to that after exposure for two hours to 10-20 ppm in the air.

Using ^{38}Cl-labeled halogenated hydrocarbons, Morgan et al. (1970) compared the blood-air partition coefficient, solubility, and excretion rates of various halogenated hydrocarbons (Table III-2). For the excretion studies, approximately 5 mg of labeled material was administered by a single breath inhalation to human subjects. The subjects held their breath for 20 seconds to ensure maximum absorption. Exhaled air was trapped in granulated charcoal and the radioactivity in the charcoal

Table III-2 Physical Properties and Absorption of Inhaled Vapors[a]

Compound	Blood/Air Partition Coefficients	Solubility (g/100 ml water)	Total Excretion in Breath After 1 hour as Percent of Dose
Methyl Chloroform	1.4	0.44	44
1,1,2-Trichloroethane	44.2	0.44	2.9
1,1,2-Trichloroethylene	9.5	0.10	10

[a] Adapted from Morgan et al. (1970).

traps was measured by gamma-ray scintillation spectrometry. In comparison to other halogens, the amount of methyl chloroform which was excreted was very high, indicating a low level of retention. Urinary excretion of total ^{38}Cl was less than 0.01 percent per minute with most compounds.

The uptake of non-labeled methyl chloroform from air containing 0, 100, 350, and 500 ppm of the compound was studied in 20 male and female subjects by Stewart et al. (1975). Subjects were exposed to each concentration for 1, 3, and 7.5 hours. Breath samples were taken from 1 minute to 71 hours after exposure, and were analyzed for unmetabolized compound. Curves of the methyl chloroform remaining in the breath were plotted to estimate the magnitude of exposure. Breathing 350 ppm methyl chloroform for 1 hour, for example, produces a breath level of about 165 ppm, which declines to under 1 ppm at 23 hours. On the other hand, breathing the same concentration (350 ppm) for 7.5 hours gives a breath concentration of approximately 244 ppm which declined to approximately 7 ppm after 16 hours. The authors found that the rate of methyl chloroform excretion was a function of exposure duration. The data generated a family of post-exposure breath decay curves that could be used to estimate the magnitude of exposure.

Stewart et al. (1961) measured human urine samples following 15 minutes of exposure to methyl chloroform; some samples contained up to 2 ppm of the compound, some contained only a trace, and some urine samples contained none at all.

Morgan et al. (1970) demonstrated that in man, the amount of absorption of methyl chloroform is increased by inhaling the vapor and holding the breath.

Summary

Absorption of methyl chloroform is most commonly experienced in man primarily via inhalation, and secondarily through dermal absorption. The rate of absorption during exposure possibly affects the toxic potential of the specific chlorinated hydrocarbon in question.

2. Distribution

Holmberg et al. (1977), studied the distribution of methyl chloroform in mice during and after inhalation. Solvent concentrations in the kidney and brain were about the same at a given exposure concentration, but concentrations in the liver were twice those observed in the kidney and brain following exposures to 100 ppm or more (Table III-3). A pharmacokinetic model with both uptake and elimination of the first order best fitted the empirical data. Hake et al. (1960) reported that 0.09 percent of a large dose of methyl chloroform was retained in the skin of rats as the parent compound after

Table III-3 Concentrations of Methyl Chloroform in Tissues of Mice Following Inhalation Exposures*

Concentration (ppm)	Exposure Time (h)	1,1,1-Trichloroethane Concentration (ug/g tissue) Blood	Liver	Kidney	Brain
10	24	0.6 ± 0.16 a/	1.5 ± 0.3	1.1 + 0.2	0.8 ± 0.1
100	24	6.3 ± 3.0	12.2 ± 4.6	5.9 ± 2.2	6.2 ± 1.3
1,000	6	36 ± 16	107 ± 38	60 ± 16	57 ± 17
5,000	3	165 ± 25	754 ± 226	153 + 27	156 ± 24
10,000	6	404 + 158	1429 ± 418	752 ± 251	739 + 170

a/ Mean ± SDM

*Adapted from Holmberg et al. (1977).

25 hours of administration of an intraperitoneal (I.P.) dose (700 mg per kg). The blood contained 0.02 percent, the fat 0.02 percent and other sites 0.1 percent of the dose administered. The blood, body fat, and other sites contained 0.02, 0.02, and 0.1% of the administered dose, respectively.

Astrand et al. (1973) and Astrand (1975) found that the uptake of methyl chloroform and other solvents into the alveolar air and arterial blood was dependent on pulmonary ventilation and blood circulation which are affected by the intensity of physical work. In these experiments, 12 men (ages 21-28) were treated for 30 minutes with 250 ppm or 350 ppm of methyl chloroform during rest and exercise (50-150 watts, a unit of workload as measured on a bicycle ergometer).

The concentration of the chemical in the alveolar air (180 ppm) and arterial blood (5 ppm) was nearly the same at an exposure of 350 ppm at rest and at 250 ppm during light exercise. Monster et al. (1979) exposed six male human volunteers (ages 27-34) for four hours to 70 ppm methyl chloroform at rest, 145 ppm at rest, and 142 ppm at rest combined with work loads (two times 30 minutes, 100 watts). During the work load, the lung clearance of methyl chloroform increased 2-3 times the value at rest. In the post-exposure period, the concentration of methyl chloroform in exhaled air paralleled that in blood; the concentration of the chemical in the blood was 8.2 ± 2.5 times higher than that in exhaled air. There was no significant difference in the concentration of the chemical in the blood or exhaled air of subjects in the rest group (145 ppm exposure) and that in the rest/work group (142 ppm exposure). The slopes of the concentration curves in blood and exhaled air at 20 hours, 50 hours and 100 hours after exposure corresponded to a half-life of methyl chloroform of about 9 hours, 20 hours, and 26 hours, respectively.

Four male Sprague-Dawley rats were exposed to 955 ppm of methyl chloroform for 73 minutes, and the concentration measured in the breath until it was undetectable (Boettner and Muranko, 1969). Stewart et al. (1961) had exposed humans to similiar levels and compared the data. One hour following exposure, human breath contained 1.85 times the concentration Table III-3 of methyl chloroform as that in rat-expired air; 10 hours following exposure, human breath contained four times the concentration in rat-expired air. These results showed that humans and rats differ in any or all of the parameters of absorption, elimination, or retention. However, it is important to note that species metabolize methyl chloroform to a very limited extent.

Concentrations of methyl chloroform in the expired air sample of rats and man were compared at 1 hour following different exposure indices, usually calculated as the product of concentration and time (Stewart et al. 1961). The results indicated that the concentration of the solvent was of greater importance than the elapsed time from inhalation in determining post-exposure breath concentration. Additional studies with concentrations from 100 to 1,000 ppm confirmed that when the concentration of the chlorinated hydrocarbon is sufficient to cause rapid saturation, the concentration of methyl chloroform or total chlorinated hydrocarbon in expired air is proportional to the concentration of the compound rather than the time of treatment, once the saturation limit is reached.

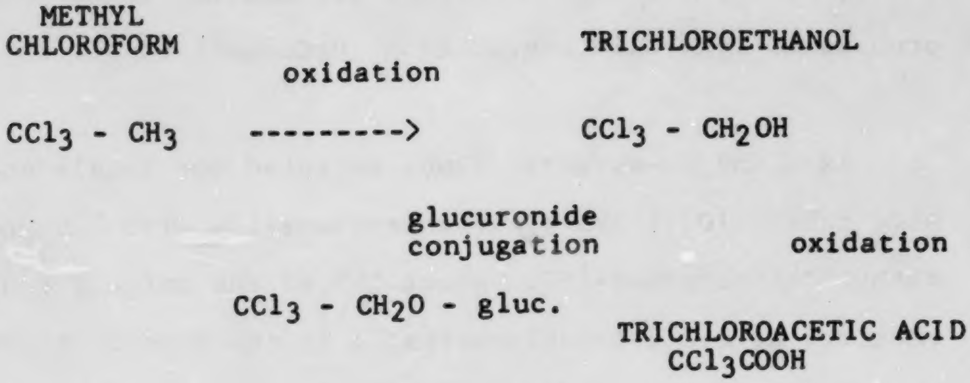
Summary

Autopsies of humans dying from acute exposure of methyl chloroform, reveal tissue concentrations according to the following order: liver > brain > kidney > muscles > lung > blood. In pregnant animal studies, methyl chloroform is readily absorbed (both inhaled and ingested) by the fetuses. Comparison studies of rat and human responses indicate that both species differ in parameters of absorption, elimination, or retention of methyl chloroform. However, it is important to note that rat and human metabolize methyl chloroform to a very limited extent.

3. Biotransformation

The primary metabolites of methyl chloroform are trichloroethanol and trichloroacetic acid (TCA) as shown in Figure III-1 (Hake et al. 1960 Ikeda and Ohusuji 1972).

Figure III-1 Metabolic Route Suggested for Methyl Choloroform


METHYL CHLOROFORM
TRICHLOROETHANOL
oxidation
$CCl_3 - CH_3$
--------->
$CCl_3 - CH_2OH$
glucuronide conjugation
oxidation
$CCl_3 - CH_2O$ - gluc.
TRICHLOROACETIC ACID
CCl_3COOH

Adapted from Hake et al. (1960), Ikeda and Ohtsuji (1972).

On the basis of *in vitro* experiments with normal gut flora, it appears that microbial degradation is not an important process in metabolic degradation (McConnell et al. 1975).

Hake and co-workers (1960) injected one female and two male rats (170 to 183 g) intraperitoneally with 700 mg/kg of methyl chloroform-1-^{14}C. About 50% of the urinary radioactivity occurred as 2,2,2-trichloroethanol in the form of glucuronide conjugate. The other 50% volatilized at room temperature. It was suggested that methyl chloroform metabolized by an initial oxidation to trichloroethanol and subsequent oxidation to small quantities of trichloroacetic acid. In this study, 98.7% of the injected radioactivity was exhaled as unchanged compound, and 0.5% as $^{14}CO_2$. Only 0.85% of injected radioactivity was recovered in urine, and only half of that was identified as a metabolite, indicating insignificant bioaccumulation.

The studies on metabolism by Ikeda and Ohtsuji (1972) compared the metabolism of methyl chloroform using both inhalation dosage (a route of greater interest to human work) and i.p. injection of 200 ppm for 8 hours. Eight studies of six 50g Wistar rats per study were used. All urine excreted in 48 hours was collected. Trichloroacetic acid (0.5 mg/kg body weight) and trichloroethanol (3.1 mg/kg body weight) were found. A dose of 2.78 mmol/kg body weight of methyl chloroform was also injected i.p. into a similar group of rats to check the effects of the dosage route. The results of the urine analysis following i.p. injection were essentially the same as those obtained on the inhalation experiments. The relative levels of trichloroethanol and trichloroacetic acid seen in Ikeda's experiments may indicate that the acid is derived from the alcohol.

Fukabori and co-workers (1976) reported the metabolism of methyl chloroform in humans after skin application to two sites.

Site I

Forearm skin, 2 hr/day for 5 days
Metabolites in urine: Trichloroethanol, 2 to 6 mg/day (Day 1)
Trichloroacetic acid, slight increase with increased exposure

Site II

Dip both hands, seven times per day for 4 days,
Metabolite in urine: Trichloroethanol, 5 to 15 mg/day

It should be noted that most of the methyl chloroform was in the expired air. The concentrations of the unchanged solvent ranged from 5 to 11 ppm (days 1 and 4) respectively, when hands were dipped in the solvent.

Summary

Trichloroethanol and trichloroacetic acid are the primary metabolites of methyl chloroform. Various metabolic studies in animals of methyl chloroform have been cited noting that regardless of dosage route (inhalation or ingestion) the results of urine analysis were essentially the same. Human metabolic profiles after skin application of methyl chloroform indicate both trichloroethanol and trichloroacetic acid (increasing slightly with an increased exposure) in urine. However, most methyl chloroform was found unchanged (98.7%) in the expired air.

4. Excretion

Pulmonary excretion rates in man in the first hour following exposure to methyl chloroform were 44% (Morgan et al. 1970). In a series of chlorinated compounds, excretion rates were inversely proportional to the lipid solubility of the compound.

A summary of the excretion of methyl chloroform in expired air sample is given in Table III-4.

In the studies of Hake et al. (1960), over 99% of the i.p.-injected methyl chloroform was excreted by rats via the pulmonary route (98.7% unchanged, 0.5% metabolized) and less than

Table III-4 Methyl Chloroform Excretion in Exhaled Breath

Route	Species	% Dose exhaled unmetabolized	Reference
Skin contact	Humans	Peak breath level = 14% of estimated 150 ppm dose	Stewart and Dodd (1964)
Inhalation	Humans	44% in 1 hour	Morgan et al. (1970)
Injection (i.p.)	Rats	> 99% of 77 mg/kg	Hake et al. (1960)

1% via the urine (0.85% of dose, half identified as the glucuronide of trichloroethanol). Boettner and Muranko (1969) have used animal pulmonary excretion data for estimation of exposure in humans.

Ikeda and Ohusuji (1972) compared the metabolism of methyl chloroform after exposing Wistar rats (70 g body weight) of both sexes to the vapor (200 ppm for eight hours) and after intraperitoneal injection (2.78 mmole/kg). Urine was collected for 48 hours. The total trichloro-compounds were estimated colorimetrically by Fujiwara reaction after oxidation of the urine. Trichloroacetic acid (TCA) was determined by the same colorimetric method without oxidation. The difference between the total trichloro-compounds (after oxidation) and TCA (without oxidation) was calculated to be trichloroethanol (TCE). Regardless of the role of administration of methyl chloroform, 48-hour urine samples contained 0.5 mg/kg (body weight) of TCA and 3.1 mg/kg of TCE.

The publication of recent technical reports on the pharmacokinetics of methyl chloroform provide the disposition characteristics of the chemical in rats and mice (Schumann et al. 1982a, 1982b). The animals were exposed via inhalation to 150 or 1,500 ppm of radiolabeled material for 6 hours. The elimination of the radioactivity was measured for 72 hours. Following exposure to 150 or 1,500 ppm, both species excreted greater than 96% of administered radioactivity during the first

24 hours. The primary route of elimination from the body was via exhalation of unchanged methyl chloroform. In the rat, approximately 94% and 98% of the total administered radioactivity was eliminated in expired air after exposure to 150 or 1,500 ppm, respectively. In the mice, the percentages were 87% and 97% of the respective exposure concentrations. The remaining radioactivity was detected as CO_2 in the expired air and as nonvolatile radioactivity in urine, feces, carcass and cage wash. Mice were found to metabolize two or three times more methyl chloroform on a body weight basis compared to rats. The authors stated that (1) since the biotransformation of methyl chloroform occured to such a limited extent, saturation of its metabolism did not impair markedly on the distribution or elimination of the parent chemical, (2) the body burden, end-exposure blood level, and tissue concentration of methyl chloroform were found overall to increase in direct proportion with the exposure level, and (3) radiolabeled methyl chloroform was more concentrated in the fat of both species than in the liver or kidneys immediately after exposure (however it was rapidly cleared from the fat so that by 24 hr $< 2\%$ of the initial radioactivity remained).

Morgan et al. (1970) measured pulmonary excretion of ^{38}Cl-labeled methyl chloroform and trichloroethylene in man following a single breath administration; the former was expired more rapidly than the latter during the first hour (i.e., 44% and 10% of the inhaled dose).

With low level exposure (about 183 ppm), Monzani et al. (1969) observed that (a) only one of 18 workers excreted trichloroacetic acid in the urine, and (b) that excretion was at a level of 9.72% mg/liter of urine.

In 1968, Tada and co-workers exposed two male subjects by inhalation to a series of chlorinated hydrocarbons. The urinary excretion of trichloroacetic acid was increased by repeated exposures. However, the increase was not proportional to vapor concentration and exposure duration.

Tada (1969) repeatedly exposed humans to 200-400 ppm methyl chloroform. There was an increase in urinary excretion of trichloroacetic acid with a maximum reached in 4-5 days. The urinary acid levels fluctuated during the day; the author suggested that the total 24-hour excretion was related to time and intensity (vapor concentration) of exposure.

Methyl chloroform was still found at a level of 0.1 ppm in the breath of an individual after 1 month of exposure to a mixture of 370 ppm of the compound and 130 ppm trichloroethylene, 7 hours/day for 5 days (~~Stewart et al~~ Rowe et al. ~~1969~~ 1963). Methyl chloroform was also present in alveolar air 1 month after exposure to concentrations ranging from 420-612 ppm for 6.5 to 7 hours/day for 5 days (Stewart et al. 1961).

Summary

Methyl chloroform and its metabolite (identified and unidentified) have been shown to be excreted (unchanged) in man and rats via the lungs and urine. In rats, methyl chloroform has been administered by 2 routes, inhalation and intraperitoneal injection. Alveolar air was the main route of excretion in both cases. Clinical studies indicate that exposure to methyl chloroform and resulting urinary levels of trichloroacetic acid are related to time and intensity of exposure.

B. Pharmacodynamic Effects (Animal and Human)

Like other halogenated hydrocarbons, methyl chloroform influences the functions of the CNS, heart, lungs, liver and kidneys.

1. Central Nervous System (CNS) Effects

In the late 1800's, methyl chloroform was considered superior to chloroform because it produces general anesthesia with minimal excitation and salivation. Lazarew (1929) determined the concentration causing complete narcosis to be 45 mg/l and the minimal fatal concentration 65 mg/l. The ratio between the concentration of the vapor causing the death and that producing the loss of reflexes and that producing death in mice was found to be 20, as compared with 15 for chloroform.

Kranz et al. (1959) estimated the dosage in dogs to be 0.45 g/kg for induction of anesthesia and 0.80 g/kg for causing respiratory failure. The anesthetic index of methyl chloroform was 1.77 for dogs and 2.15 for monkeys, which provide greater margins of safety than those of chloroform. Dornette and Jones (1960) used 1% to 2.6% methyl chloroform (10,212 to 26,500 ppm) with 80% nitrous oxide for anesthesia induction in 50 human subjects. The volunteers were kept anesthetized up to 2 hours, maintained with increased methyl chloroform levels of 0.6%-2.25% (6,127 to 22,982 ppm), administered with decreased nitrous oxide-oxygen. The investigators attributed 75% of the anesthetic effect to methyl chloroform and the remaining to nitrous oxide-oxygen mixture. Light anesthesia was induced within 2 minutes, and recovery of reflexes occurred 3 to 5 minutes after discontinuing the anesthetic agent. Siebecker et al. (1960) studied the human electroencephalogram (EEG)in methyl chloroform (plus nitrous oxide) anesthesia and found patterns similar to halothane.

The Romberg test (a neurological test that measures proprioceptive control with a subject standing, feet together, eyes closed) has been used to measure the narcotic or anestheticlike effects of methyl chloroform. Stewart et al. (1961) found 6 subjects failed to perform a normal test after

15 minutes exposure at 2,650 ppm (starting at zero concentration), but noted no CNS effects at 500 ppm. Torkelson et al. (1958) found positive Romberg tests in all three subjects exposed to methyl chloroform at 1,740-2,180 ppm. Lightheadedness occurred in three of the four subjects exposed to 1,000 ppm for 70-75 minutes.

Chemical tests of motor reflex have demonstrated reversible narcotic effects by methyl chloroform in human subjects exposed to 250 ppm (Gambarale and Hultengren, 1973), 450 ppm (Salvini et al. 1971), 1,000 ppm for 70 to 75 minutes (Torkelson et al. 1958), and to 900 ppm for 20 to 73 minutes (Stewart et al. 1961). Stewart et al. (1961) found no CNS effects with balance and coordination tests following methyl chloroform exposure at 500 ppm for 3 hours, but observed CNS effects in four of the five subjects exposed at the same level for a longer time (6.5 to 7 hours) (Stewart et al. 1969).

Stahl et al. (1969) reviewed six fatal cases of exposure; autopsy samples showed the concentration of solvent to be: 0.32; 2.7; 9.3; 50.0; 56.0; and 59.0 milligrams per 100 g brain tissue. Kleinfeld and Feiner (1966) noted high, but unquantitated, levels in brain after a death from methyl chloroform.

Summary

The Romberg test (a neurological test which measures proprioceptive control) has been used to measure the narcotic effects of methyl chloroform within the range from 500 ppm (no CNS effects) to 2,650 ppm. Impairment in motor control after exposure to methyl chloroform has been demonstrated in humans with concentrations as low as 250 ppm, but CNS effects appear to be dependent on methyl chloroform concentration as well as exposure time. Human autopsies following death due to methyl chloroform show high, but unquantitated levels of methyl chloroform in brain tissues.

2. Cardiotoxicity

The proarrhythmic activity of methyl chloroform has been investigated in the dog. Administration of methyl chloroform to two dogs to induce anesthesia without premedication was reported by Renmick et al. (1949) to have resulted in sudden death. Further experiments with five dogs under barbital anesthesia showed that ventricular extrasystoles and ventricular tachycardia were regular occurrence when epinephrine was injected after administration of repeated small doses of methyl chloroform. Maximum sensitization of the heart occurred after administration of 0.25-0.40 ml/kg of methyl chloroform; greater amounts raised the threshold dose of epinephrine, partly because of severe hypotension. They concluded that epinephrine itself, however, is known to induce ventricular extrasystoles and tachycardia, and the effects noted may have been due, at least in part, to epinephrine. Reinhardt et al. (1973) found the minimal concentration that causes sensitization in the dog to be 27.8 mg/l. The effective concentration was 40.7 mg/l in another group of dogs examined by Clark and Tinston (1973).

Somani and Lum (1965) and Lucchesi (1965) administered 133.6 mg/kg of methyl chloroform intratracheally and injected epinephrine (10 ug/kg) intravenously. This combination caused ventricular fibrillation. However, dogs pretreated with a beta-adrenergic blocking agent failed to exhibit any cardiotoxic effects.

The death of a young seaman due to methyl chloroform abuse resulted in cardiac changes (Travers, 1974). Progressive hypotension and bradycardia and several instances of cardiac arrest resulted in death 24 hours after collapse. Autopsy showed right atrial and ventricular dilatation.

Inhalation of high levels of methyl chloroform produces a decrease in heart rate and blood pressure during the first few minutes of exposure. These effects have been reported at 6,250 ppm for rabbits (Truhaut et al. 1972); 8,000 ppm for dogs (Herd et al. 1974); 25,000 and 50,000 ppm for monkeys (Belej et al. 1974).

Cellular hypertrophy in the tissues following methyl chloroform exposure (which is a sign of cardiovascular toxicity) has been reported in several studies (Griffiths et al. 1972, Adams et al. 1950, Horiguchi and Horiguchi 1971, Rice et al. 1967). Human autopsy reports have mentioned tissue congestion following deaths due to methyl chloroform, expecially after prolonged abuse or high exposure (Hall and Hine 1966, Stahl et al. 1969, Hatfield and Maykoski 1970).

Summary

Methyl chloroform-induced cardiotoxicity has been found in animal experiments (dogs, rabbits, and monkeys) and in human autopsy reports, where cellular hypertrophy in the cardiac tissues following methyl chloroform abuse or high exposure has been present.

3. Hepatotoxicity and Nephrotoxicity

Liver cell damage produces an increase in cytoplasmic transaminase, followed by lactic dehydrogenase (LDH) from the mitochondria. To determine the organ source of these enzyme level changes after methyl chloroform exposure, the LDH must be electrophoretically fractionated.

Platt and Cockrill (1969) found increases in only two of seven enzymes measured in rats given methyl chloroform (1,650 mg/kg) orally in liquid paraffin for 7 days. The $NADPH_2$ -cytochrome C reductase and glutamate dehydrogenase activity of rat liver were significantly increased in the treated animals.

Klaassen and Plaa (1969) found no elevation in liver triglycerides within the first 36 hours after exposing rats to methyl chloroform at 3,800 mg/kg (75% of the LD_{50}).

Six controlled human studies showed that the urinary urobilinogen was the most sensitive test for ascertaining hepatotoxicity in subjects exposed to methyl chloroform (approximately 500 ppm or above) (Stewart et al. 1961). The serum glutamic oxaloacetic transaminase (SGOT) values and the 15 minute phenosulfonphthalein (PSP) excretion deviated somewhat from pre-exposure values, but remained within normal limits.

The lowest concentration of methyl chloroform that resulted in hepatic effects was reported by McNutt et al. (1975) who found significantly elevated triglyceride levels in mice exposed to 250 ppm for 4 and 13 weeks. MacEwen et al. (1974), however, failed to produce elevated liver triglycerides in mice exposed continuously to 250 ppm for 100 days, but observed the effects at 1,000 ppm.

Krantz et al. (1959) found no effects from methyl chloroform on phenosulfonphthalein retention time in an anesthetized dog, but repeated administration of the anesthesia resulted in hepatic pathology in one of the four rats.

Horiguchi and Horiguchi (1971) reported congestion of the liver and bile duct inflammation in male mice exposed to 1,000 ppm of methyl chloroform (2 hours, nine times).

Plaa (1976) summarized in Table III-5 work on trichloroethylene, methyl chloroform, and perchloroethylene with respect to liver toxicity. The table shows that toxicity is a function of the test used for all the halogenated compounds.

Hanasono et al. (1975) exposed male rats to 1.0 ml methyl chloroform/kg interperiotoneally 3 days after adminstration of alloxan which produced diabetes symptoms but no serum glutamic pyruvic transaminase (SGPT)or triglyceride change. The hepatotoxic effects of methyl chloroform in control and diabetic rats are evident from SGPT and trigylceride levels, observed as follows:

	SGPT (units/ml)	Triglyceride in liver (mg/g tissue)
Controls	42 ± 2	5.7 ± 0.5
Diabetic	65 ± 19	21.6 ± 13.1

Table III-5 Liver Effects of Methyl Chloroform and Other Chlorinated Hydrocarbons

Relative potency rankings of the subject halogenated hydrocarbons in mice

Compounds	24-HR LD_{50}) (mmole/kg)	Compounds	(BSP Retention ED_{50}) (mmole/kg)	Compounds	SGPT Elevation ED_{50}) (mmole/kg)
Trichloroethylene	24	Trichloroethylene	23	Methyl chloroform	2.5
Perchloroethylene	28	Methyl chloroform	27	Trichloroethylene	18
Methyl chloroform	37	Perchloroethylene	32	Perchloroethylene	28

Potency ratios of the three subject solvents for SGPT elevation or BSP retention in mice

Compound	BSP Retention potency ratio (LD_{50}/ED_{50})	SGPT Elevation potency ratio (LD_{50}/ED_{50})
Methyl chloroform	1.4	1.5
Trichloroethylene	1.0	1.3
Perchloroethylene	0.9	1.0

continued -

Table III-5 - continued

Severity of liver injury induced by minimal lethal doses of the three subject solvents; SGPT elevation being used as the index of hepatic dysfunction[a].

Compound	SGPT (R-F units)	
	Dogs	Mice
Perchloroethylene	400	Nil
Methyl chloroform	350	65
Trichloroethylene	250	90

[a] The ranking is: most potent first and least potent last.

Adapted from Plaa (1976).

Rice et al. (1967) gave rats methyl chloroform (2 ml/kg) 24 hours before performing hemodynamic measurements on the isolated, perfused livers. Under in vitro conditions, hepatic blood flow was not changed by the pre-treatment, although carbon tetrachloride did change blood flow characteristics in the same experimental series. A subcapsular inflammatory reaction was found in the livers of animals pretreated with methyl chloroform.

Using in vitro experimental conditions, Fuller et al. (1970) found an increase in the metabolism of hexobarbital, meprobamate, and zoxazolamine in rats following the inhalation of methyl chloroform (2,500 to 3,000 ppm) for 24 hours. There was an increase in vitro of the metabolism of these three compounds by hepatic microsomal enzymes under the influence of methyl chloroform.

The inhalation of methyl chloroform at a level of approximately 10,000 ppm for 4 to 6 hours had no effect on liver function of ethanol-exposed rats, although other chlorinated/ hydrocarbons exhibited increased hepatotoxicity (Cornish and Adefuin, 1966). Cornish et al. (1973) also failed to demonstrate increased hepatotoxicity due to methyl chloroform in rats pretreated with phenobarbital. Carbon tetrachloride was more hepatotoxic in the phenobarbital-treated rats.

Ingestion of ethanol was reported by Klaassen and Plaa (1966) to increase the hepatotoxicity of methyl chloroform. Ethanol (60%) was administered by gavage at doses of 5 mg/kg. In one experiment, a dose of ethanol was given on each of 3 days before intraperitoneal administration of methyl chloroform in corn oil (0.02 ml/g) at doses of 2.5-2.75 ml/kg. In another experiment, a single dose of ethanol was given 12 hours before the methyl chloroform. In both experiments, BSP retention was significantly higher in the ethanol pre-treated rats than in control rats given only methyl chloroform. SGPT activity was not affected in this experiment by methyl chloroform at a dose of 2.5 ml/kg with or without alcohol pre-treatment, and kidney function as measured by PSP excretion was similarly not affected by methyl chloroform doses of 2.0 ml/kg. SGPT activity was also not different from controls in dogs given methyl chloroform doses of 0.85 ml/kg, with or without ethanol pre-treatment (Klaassen and Plaa 1967).

Isopropyl alcohol or acetone administered by gavage to male Swiss-Webster mice 18 hours before i.p. injection of methyl chloroform did not alter the response of SGPT activity to the administered methyl chloroform (Traiger and Plaa, 1974). The doses of methyl chloroform used in this experiment were 1.0, 2.0 and 2.5 ml/kg. The latter dose caused increases in SGPT activity, but the increases were not affected by isopropyl alcohol or acetone pretreatment.

In laboratory animals, liver function appears to be influenced by methyl chloroform. Klaassen and Plaa (1967) reported disturbances in liver functions in dogs. Similarly, rabbits exhibited hepatic function changes.

Adams et al. (1950) reported no adverse effects in guinea pigs given 1,500 ppm of methyl chloroform for 7 hours/day for 3 months. Conversely, Torkelson et al. (1958) reported liver effects in animals exposed to both 1,000 and 2,000 ppm levels of methyl chloroform for 30 to 90 minutes/day for 3 months. Klaassen and Plaa (1966) noted enlargement of hepatocytes with cellular infiltration and vacuolation in mice following methyl chloroform treatment. Slight hepatic narcosis occurred only when the dosage was in the lethal range. Von Oettingen (1964) suggested that the mechanism of hepatic changes is a function of the lipid solubility of the methyl chloroform.

Signs of hepatic effects include retention of BSP and change in SGPT activity following injection or inhalation of methyl chloroform. Gehring (1968) found the ED_{50} for SGPT activity was 2.91 g/kg in mice, whereas Klaassen and Plaa (1966) found a value of 3.34 g/kg for the same effect. The inhalation ED_{50} for SGPT activity in mice was 13,662 ppm for approximately 10 hours (Gehring, 1968).

Plaa and Larson (1965) reported that only one of the nine mice given methyl chloroform (3,400 mg i.p./kg) exhibited significant proteinurea. In another trial, mice exhibited swelling of the convoluted tubules of the kidney after a similar dose of methyl chloroform. However, no necrosis was observed in these studies. Renal toxicity (Klaassen and Plaa, 1966). These authors studied renal function patterns in dogs exposed to methyl chloroform and found renal changes as determined by phenolsulfonphthalein glucose, and protein excetion data, but no histopathological changes (Klaassen and Plaa, 1967). According to these data, the kidney is less affected by methyl chloroform than the liver.

Stewart (1971) reported several instances of apparent kidney toxicity related to methyl chloroform exposure in humans. According to a human ingestion study, elevated serum bilirubin and evidence of kidney injury associated with hematuria and proteinurea were seen. In other studies exposures to the solvent (900 ppm for 20 minutes) produced elevated urinary urobilinogen in one subject, and some evidence of adverse effects on kidneys (dye clearance rate, hematuria) was observed in six subjects after exposure to 500 ppm of methyl chloroform for 78 minutes. Five of the seven subjects exposed to methyl chloroform (0 to 2,650 ppm) for 15 minutes exhibited a few erythrocytes in the urine and/or a positive urinary urobilinogen (Stewart et al. 1961).

Summary

Various experiments using rats, dogs, and mice to determine the influence of methyl chloroform on liver function provide conflicting results due to variation in animal species, dose, and treatment schedule. For example, guinea pig experiments have shown: 1) no organ damage following exposure to 1,500 ppm of methyl chloroform for 7 hours/day for 3 months, and again, 2) liver damage due to 1,000 ppm of methyl chloroform for 30 to 90 minutes/day for 3 months.

Nephrotoxicity, as measured by tubular damage, PSP, glucose, and protein excretion data has been investigated in animals and man with reference to exposure to methyl chloroform. Although some kidney damage in laboratory animals has been reported, it appears that methyl chloroform affects the liver before it damages the kidneys.

4. Pneumotoxicity

Irritation of the lungs and respiratory tract as a result of methyl chloroform inhalation has been observed in industrial workers and experimental animals (Stewart et al. 1961, 1969, Salvini et al. 1971). Humans occupationally exposed to methyl chloroform by inhalation and skin contact for prolonged periods complained of irritation of the upper respiratory tract (Weitbrecht 1965). American industrial workers, who were chronically exposed to the compound at low levels also have complained of respiratory tract irritation (Vandervort and Thoburn 1975, Hervin 1975). Nearly all National Institute for Occupational Safety and Health Hazard Evaluation Reports on methyl chloroform, when instituted by worker complaint, were due to strong solvent odor and throat irritation (1978). In nearly all cases the levels in ambient air were far below the maximum allowable concentrations. There is no idication in the literature that the lungs of man or animals become hypersensitive following repeated inhalation, but the irritation is apparently a matter of concern.

In animal studies, structural changes in the lungs were seen in guinea pigs exposed to 1,000 ppm of methyl chloroform for 72 minutes/day (69 exposures), and to 2,000 ppm for 12 minutes/day for 69 exposures. On the other hand, 1,000 ppm for 36 minutes/day (69 exposures) produced no lung irritation (Torkelson et al. 1958). Prendergast et al. (1967) exposed several animal species to 370 ppm of methyl chloroform continuously for 90 days but observed only non-specific inflammatory changes in the lungs.

MacEwen and Vernot (1974) reported that the most significant effect seen in rats continuously exposed to methyl chloroform by inhalation for 100 days was respiratory disease. Lung changes were seen in approximately half of the rats exposed to 250 and 1,000 ppm.

Pulmonary congestion in animal inhalation experiments has been widely reported, particularly for chronic (or high-level) exposures to methyl chloroform (Horiguchi and Horiguchi 1971). Pulmonary edema and congestion, however, are consistent with cardiovascular insufficiency rather than primary lung effects. The lung effects appear to be limited to irritation, and are reported to be transitory in humans, even following moderately high exposures to the compound (Weitbrecht 1965).

Summary

The possibility of increased pneumotoxicity due to "additive" exposure to various levels of methyl chloroform from food and drinking water contamination has not been quantified. However, the effects of the compound through ingestion would be less severe than effects from inhalation since the small amount of compound is eliminated via the gastrointestinal tract in the urine and feces.

IV. HUMAN EXPOSURE

Humans may be exposed to 1,1,1-trichloroethane in drinking water, food, and air. Detailed information concerning the occurrence of and exposure to 1,1,1-trichloroethane in the environment is presented in another document entitled "Occurrence of 1,1,1-Trichloroethane in Drinking Water, Food, and Air" (Letkiewicz et al. 1983). This section summarizes the pertinent information presented in that document in order to assess the relative source contribution from drinking water, food, and air.

Exposure Estimation

This analysis is limited to drinking water, food, and air, since these media are considered to be general sources common to all individuals. Some individuals may be exposed to 1,1,1-trichloroethane from sources other than the three considered here, notably in occupational settings and from the use of consumer products containing 1,1,1-trichloroethane. Even in limiting the analysis to these three sources, it must be recognized that individual exposure will vary widely based on many personal choices and several factors over which there is little control. Where one lives, works, and travels, what one eats, and physiologic characteristics related to age, sex, and health status can all profoundly affect daily exposure and intake. Individuals living in the same neighborhood or even in the same household can experience vastly different exposure patterns.

Unfortunately, data and methods to estimate exposure of identifiable population subgroups from all sources simultaneously have not yet been developed. To the extent possible, estimates are provided of the number of individuals exposed to each medium at various 1,1,1-trichloroethane concentrations. The 70-kg male is used for estimating intake.

A. Water

Cumulative estimates of the U.S. populations exposed to various 1,1,1-trichloroethane levels in drinking water from public drinking water systems are presented in Table IV-1. The values in the table were obtained using Federal Reporting Data Systems data on populations served by primary water supply systems (FRDS 1983) and the estimated number of these water systems that contain a given level of 1,1,1-trichloroethane. An estimated 9,524,000 individuals (4.4% of the population of 214,419,000 using public water supplies) are exposed to levels of 1,1,1-trichloroethane in drinking water at or above 0.5 ug/1, while 417,000 individuals (0.2%) are exposed to levels above 5 ug/1. It is estimated that 180,000 individuals are exposed to levels greater than 100 ug/1. Of the approximately 9.1 million individuals exposed to levels ranging from 0.5 to the same household can experience vastly different exposure patterns.

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Table IV-1 Total Estimated Cumulative Population (in Thousands) Exposed to 1,1,1-Trichloroethane in Drinking Water Exceeding the Indicated Concentration

	Number of people served in U.S.	Cumulative population (thousands) exposed to concentrations (ug/l) of:											
System type	(thousands)	≥0.5	>5	>10	>20	>30	>40	>50	>60	>70	>80	>90	>100
Groundwater	73,473	3,732	417	275	227	180	180	180	180	180	180	180	180
Surface water	140,946	5,792	0	0	0	0	0	0	0	0	0	0	0
Total	214,419	9,524	417	275	227	180	180	180	180	180	180	180	180
(% of total)	(100%)	(4.4%)	(0.2%)	(0.1%)	(0.1%)	(0.1%)	(0.1%)	(0.1%)	(0.1%)	(0.1%)	(0.1%)	(0.1%)	(0.1%)

5 ug/1, 5.8 million (64%) obtain water from surface water supplies. All exposure to 1,1,1-trichloroethane in drinking water at levels above 5 ug/1 is expected to be from groundwater sources.

No data were obtained on regional variations in the concentration of 1,1,1-trichloroethane in drinking water. Discharges to the environment during use in metal cleaning operations and use of drain cleaners are expected to be primary causes of drinking water contamination. The highest concentrations of 1,1,1-trichloroethane would be expected near sites of these uses.

Daily intake levels of 1,1,1-trichloroethane from drinking water were estimated using various exposure levels and the assumptions presented in Table IV-2. The data in the table suggest that the majority of the persons using public drinking water supplies would be exposed to intake levels below 0.014 ug/kg/day.

An indication of the overall exposure of the total population to 1,1,1-trichloroethane can be obtained through the calculation of population-concentration values. These values are a summation of the individual levels of 1,1,1-trichloroethane to which each member of the population is exposed. An explanation of the derivation of these values is presented in Appendix C. Population-concentration estimates

Table IV-2 Estimated Drinking Water Intake of 1,1,1-Trichloroethane

Exposure level (ug/1)	Persons using supplies exposed to indicated levels: Population	Persons using supplies exposed to indicated levels: % of Total population	Intake (ug/kg/day)
≥0.5	9,524,000	4.4%	≥0.014
>5.0	417,000	0.2%	>0.14
>10	275,000	0.1%	>0.29
>20	227,000	0.1%	>0.57
>100	180,000	0.1%	>2.9

Assumptions: 70-kg man, 2 liters of water/day.

for 1,1,1-trichloroethane in drinking water were 3.2×10^7 ug/1 x persons (best case), 5.5×10^7 ug/1 x persons (mean best case), 1.5×10^8 ug/1 x persons (mean worst case), and 1.8×10^8 ug/1 x persons (worst case).

Assuming a consumption rate of 2 liters of water/day, population-exposure values of 6.4×10^7 ug/day x persons (best case), 1.1×10^8 ug/day x persons (mean best case), 3.0×10^8 ug/day x persons (mean worst case), and 3.6×10^8 ug/day x persons (worst case) were derived.

B. Diet

The U.S. dietary intake of 1,1,1-trichloroethane was estimated using data on levels of 1,1,1-trichloroethane in composite samples for various food classes from the TEAM survey (Pellizzari et al. 1982). Since the majority of the TEAM samples were negative for 1,1,1-trichloroethane, the data were averaged in two ways: the negative samples were assigned the value of the limit of quantitation (maximum estimate) or the value of zero (minimum estimate). These data were expressed as daily intake by use of FDA data on food consumption by food class (FDA 1980). The estimated adult dietary intake of 1,1,1-trichloroethane for the food classes studied was found to be 0.51-7 ug/day (Table IV-3).

Table IV-3 Estimated Adult Dietary Intake of 1,1,1-Trichloroethane by Food Class[a] Using TEAM Survey Data

Food class	Average intake of food class (kg/day)[b]	Average level of 1,1,1-trichloroethane (ug/kg)		Average intake of 1,1,1-trichloroethane (ug/day)	
		Minimum[c]	Maximum[d]	Minimum[c]	Maximum[d]
I. Dairy	0.753	0.30	5	0.23	4
II. Meat, fish, and poultry	0.262	0	7	0	2
X. Oils and fats	0.073	3.8	11	0.28	0.80
XII. Beverages	0.128[e]	0	2	0	0.3
Total				0.51	7

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[a] Eight food classes not analyzed: grains and cereals (III), potatoes (IV), leafy legume and root vegetables (V, VI, VII), garden fruits (VIII); fruits (IX); and sugars and adjuncts (XI).

[b] From FDA 1980.

[c] All nonquantifiable and trace values assumed to be equal to zero.

[d] All nonquantifiable and trace values assumed to be equal to the quantitation limit (value reported is the average of those composites with known quantitation limits).

[e] Calculated by subtracting 14-day drinking water consumption from 14-day beverage consumption (FDA 1980) and dividing by 14.

Several problems arose in the use of these data:

1) The data are limited, since food samples were obtained on only five occasions and they may not be representative of normal 1,1,1-trichloroethane levels in foods.

2) The quantitation limits were high, so significant levels in some foods may not have been quantified.

3) Only four of 12 food classes, those suspected of containing the highest levels of volatile organics, were analyzed.

4) The composite samples generally contained lower levels of 1,1,1-trichloroethane than expected from the concentrations in subcomposite samples (i.e., some 1,1,1-trichloroethane appeared to have been lost during compositing).

Because of these data limitations, the range of dietary intake values calculated from the TEAM study are considered to be approximations.

If the average adult male is assumed to weigh 70 kg, the adult dietary intake estimated from the TEAM study data is 0.0073-0.1 ug/kg/day. From this range, daily adult intake was estimated to be 0.05 ug/kg/day.

It is expected that dietary levels of 1,1,1-trichloroethane would vary somewhat with geographical location, with higher levels occurring in foods from areas near sources of 1,1,1-trichloroethane. However, because of the limited data available, no estimates of variations in intake by geographical region could be made. Variances in individual exposure due to differences in diet could not be assessed.

C. Air

Exposure to 1,1,1-trichloroethane in the atmosphere varies from one location to another. The highest level of 1,1,1-trichloroethane reported in the atmosphere was 310,000 ng/m^3 (310 ug/m^3) (Pellizzari 1979 cited in Brodzinsky and Singh 1982). High levels, averaging greater than 70,000 ng/m^3 (70 ug/m^3), have been detected in other areas. Normal levels, however, are somewhat lower. Brodzinsky and Singh (1982) calculated median air levels of 1,1,1-trichloroethane for rural/remote areas, urban/suburban areas, and source dominated areas of 600 ng/m^3 (0.60 ug/m^3), 2,800 ng/m^3 (2.8 ug/m^3), and 6,500 ng/m^3 (6.5 ug/m^3), respectively.

The monitoring data available are not sufficient to determine regional variations in exposure levels for 1,1,1-trichloroethane. However, urban and industrial areas appear to contain higher levels, as expected.

The daily respiratory intake of 1,1,1-trichloroethane from air was estimated using the assumptions presented in Table IV-IV and the median and maximum levels for 1,1,1-trichloroethane reported above. The estimates in Table IV-4 indicate that the daily 1,1,1-trichloroethane intake from air for adults in source dominated areas is approximately 2 ug/kg/day. In contrast, the intake calculated using the maximum level reported is 100 ug/kg/day; few if any persons are believed to

Table IV-4 Estimated Respiratory Intake of 1,1,1-Trichloroethane

Exposure (ug/m^3)	Intake (ug/kg/day)
Rural/remote (0.60)	0.20
Urban/suburban (2.8)	0.92
Source dominated (6.5)	2.1
Maximum (310)	100

Assumptions: 70-kg man, 23 m^3 of air inhaled/day (ICRP 1975).

be exposed at that level. The values presented do not account for variances in individual exposure or uncertainties in the assumptions used to estimate exposure.

In addition to the available monitoring data, estimates of atmospheric levels of 1,1,1-trichloroethane have been prepared by applying air dispersion models to 1,1,1-trichloroethane emission sources (Systems Applications 1982). The computed average concentrations of 1,1,1-trichloroethane and the number of persons estimated to be exposed to these concentrations are presented in Table IV-5. Specific point sources are individually identified sources with known locations and modes and rates of emissions. These are generally manufacturing facilities. General point sources are those which are numerous, small, or of uncertain location, but can produce isolated patterns of significant concentration. Area sources are numerous and emit only small concentrations of the chemical (for instance, home chimneys, automobiles). These estimates indicate that less than 14 million people are exposed to airborne 1,1,1-trichloroethane at concentrations in excess of 2.5 ug/m^3 (2,500 ng/m^3).

Table IV-5 also presents a total population-concentration estimate for 1,1,1-trichloroethane of 4.77×10^8 ug/m^3 x persons. Assuming an inhalation rate of 23 m^3 of air/day, a population-exposure of 1.10×10^{10} ug/day x persons was calculated.

Table IV-5 Exposure and Dosage Summary for Airborne 1,1,1-Trichloroethane

Concentration level (ug/m^3)	Population exposed (persons)				Dosage (ug/m^3 x persons)			
	Specific point source	General point source	Area source	U.S. total	Specific point source	General point source	Area source	U.S total
50	2	0	0	2	137	0	0	137
25	10	12,000	0	12,010	387	400,000	6,400,236	6,800,623
10	85	215,000	505,140	720,225	1,380	3,000,000	6,400,236	9,401,616
5	427	851,000	505,140	1,356,567	3,420	7,000,000	54,715,139	61,718,559
2.5	1,982	2,580,000	11,147,543	13,729,525	8,430	13,000,000	108,733,700	121,742,130
1	9,036	--	43,314,528	--	18,700	22,000,000	156,869,401	178,888,101
0.5	32,600	--	108,928,270	--	34,600	32,000,000	170,896,866	202,931,466
0.25	73,844	--	145,742,124	--	48,800	45,000,000	--	--
0.1	189,148	--	--	--	65,700	69,000,000	--	--
0.05	--	--	--	--	--	92,000,000	--	--
0.025	--	--	--	--	--	111,000,000	--	--
0.01	--	--	--	--	--	147,000,000	--	--
0.005	--	--	--	--	--	178,000,000	--	--
0.0025	--	--	--	--	--	204,000,000	--	--
0.001	--	--	--	--	--	229,000,000	--	--
0	461,832	--	158,679,135	--	71,300	304,000,000	173,047,000	477,118,300

Note: The use of "--" as an entry indicates that the incremental increase in the dosage or the population exposed is not significant (relative to the last entry in that column or to an entry in another column at the same row) or that the exposure of the same population may be counted in another column.

Source: Systems Applications 1982

SUMMARY

Table IV-6 presents a general view of the total amount of 1,1,1-trichloroethane received by an adult male from air, food, and drinking water. Four separate exposure levels in air, six exposure levels in drinking water, and one exposure level from foods are shown in the table.

The data presented have been selected from an infinite number of possible combinations of concentrations for the three sources. The actual exposures encountered would represent some finite subset of this infinite series of combinations. Whether exposure occurs at any specific combination of levels is not known; nor is it possible to determine the number of persons that would be exposed to 1,1,1-trichloroethane at any of the combined exposure levels. The data presented represent possible exposures based on the occurrence data and the estimated intakes.

The relative source contribution data are based on estimated intake and do not account for a possible differential absorption rate for 1,1,1-trichloroethane by route of exposure. The relative dose received may vary from the relative intake. In addition the relative effects of the chemical on the body may vary by different routes of exposure.

Brodzinsky and Singh (1982) calculated a median urban/suburban air level of 1,1,1-trichloroethane of 2.8 ug/m^3 based

Table IV-6 Estimated Intake of 1,1,1-Trichloroethane
from the Environment by Adult Males in ug/kg/day
(% from Drinking Water)

Concentration in drinking water (ug/1)	Concentration in air: Rural/remote (0.60 ug/m^3)	Urban/suburban (2.8 ug/m^3)	Source dominated (6.5 ug/m^3)	Maximum (310 ug/m^3)
0	0.25 (0%)	0.97 (0%)	2.2 (0%)	100 (0%)
0.5[a]	0.26 (5.4%)	0.98 (1.4%)	2.2 (0.6%)	100 (0.01%)
5.0[b]	0.39 (36%)	1.1 (13%)	2.3 (6.1%)	100 (0.1%)
10[c]	0.54 (54%)	1.3 (22%)	2.4 (12%)	100 (0.3%)
20[d]	0.82 (70%)	1.5 (38%)	2.7 (21%)	100 (0.6%)
100[e]	3.2 (91%)	3.9 (74%)	5.0 (58%)	100 (2.9%)

continued -

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[a] 9,524,000 individuals using public drinking water systems are estimated to be exposed to levels > 0.5 ug/1 (4.4% of population using public water supplies).

[b] 417,000 individuals using public drinking water systems are estimated to be exposed to levels > 5.0 ug/1 (0.2% of population using public water supplies).

[c] 275,000 individuals using public drinking water systems are estimated to be exposed to levels > 10 ug/1 (0.1% of population using public water supplies).

[d] 227,000 individuals using public drinking water systems are estimated to be exposed to levels > 20 ug/1 (0.1% of population using public water supplies).

[e] 180,000 individuals using public drinking water systems are estimated to be exposed to levels > 100 ug/1 (0.1% of population using public water supplies).

Table IV-6 - continued

Intake from each source (see Sections 5.1-5.3):

Water:	0.5 ug/l:	0.014 ug/kg/day
	5.0 ug/l:	0.14 ug/kg/day
	10 ug/l:	0.29 ug/kg/day
	20 ug/l:	0.57 ug/kg/day
	100 ug/l:	2.9 ug/kg/day
Air:	0.60 ug/m^3:	0.20 ug/kg/day
	2.8 ug/m^3:	0.92 ug/kg/day
	6.5 ug/m^3:	2.1 ug/kg/day
	310 ug/m^3:	100 ug/kg/day
Food:		0.05 ug/kg/day

on air monitoring data. Assuming an air level of 2.8 ug/m^3 and the estimated 1,1,1-trichloroethane intake of 0.05 ug/kg/day in foods, drinking water would be the predominant source of 1,1,1-trichloroethane exposure in the adult male at drinking water levels above 34 ug/l. An accurate assessment of the number of individuals for which drinking water is the predominant source of exposure cannot be determined from the data since specific locations containing high concentrations of 1,1,1-trichloroethane in drinking water and low concentrations of 1,1,1-trichloroethane in ambient air and food are unknown.

Population-exposure estimates for 1,1,1-trichloroethane in drinking water and air were presented previously. Estimates for drinking water ranged from 0.64-3.6 x 10^8 ug/day x persons; the estimate for ambient air was 1.10 x 10^{10} ug/day x persons. These estimates suggest that ambient air may be a greater source of exposure to 1,1,1-trichloroethane than drinking water on a general population basis. Comparison of these estimates, however, may be deceiving since the same population-exposure level can occur if: 1) a whole population is exposed to moderate levels of a chemical or 2) some segments of the same population are exposed to high levels and others to low levels. The population-exposure values presented give no indication of the relative predominance of drinking water and air as specific sources of 1,1,1-trichloroethane on a site-by-site or subpopulation basis.

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V. HEALTH EFFECTS IN ANIMALS

1. Acute Toxicity

Lazarew (1929) exposed an unspecified number of mice to methyl chloroform to determine the minimum concentration required to produce prostration, loss of reflexes and death within 2 hours of exposure (Table V-1).

Lazarew assigned toxicity ratings to the 12 compounds based on concentrations required to produce prostration. Higher indices meant greater toxicity. The index for methyl chloroform was 3.5 compared to 14 for 1,1,2-trichloroethane, meaning that the 1,1,2-isomer was 4 times as toxic as the methyl chloroform isomer. The acute oral LD_{50} for methyl chloroform, as determined in several species of animals, is reported by Torkelson et al. (1958) to range from 5.7 to 14.3 g/kg. Unfortunately, little other toxicological data involving oral ingestion are available (Lane et al. 1982). LD_{50} values that were derived upon administration of methyl chloroform by routes other than oral illustrate the difficulty in using such data to predict consequences of ingestion of the chemical. In contrast with an oral LD_{50} value of 11 g/kg in the mouse (Torkelson et al. 1958), the LD_{50} is approximately 16 g/kg for subcutaneous injection (Plaa et al. 1958) and approximately 4.9 g/kg for intraperitoneal injection (Klaassen and Plaa 1966). By administering equivalent intraperitoneal and

Table V-1 Effects of Trichloroethane Isomers on Mice

	Minimum Concentration for Response Within 2 Hours of Exposure (mg/l)		
Compound	Proneness	Loss of Reflex	Death
Methyl chloroform	40	45	65
1,1,22trichloroethane	10	15	60

Adapted from Lazarew (1929).

oral doses of carbon tetrachloride to rats, Nadeau and Marchand (1973) demonstrated that significantly higher hepatic concentrations of carbon tetrachloride and more extensive hepatotoxicity are manifested in the animals given the compound intraperitoneally.

Despite the problems that are inherent in extrapolating data from one route of chemical exposure to another, we may gain qualitative insight into the toxicity of methyl chloroform by examining information from studies in which the oral route was not used. Plaa and his colleagues found methyl chloroform to be the least hepatotoxic of a series of alkyl halocarbons that were given subcutaneously (Plaa et al. 1958) and intraperitoneally (Klaassen and Plaa 1966) to mice and intraperitoneally to dogs (Klaaassen and Plaa 1967) and rats (Klaassen and Plaa 1969). Near-lethal quantities of methyl chloroform were generally required to produce hepatotoxicity. The authors observed little to no evidence of nephrotoxicity. In contrast to methyl chloroform (ED_{50} = 2.5 ml/kg for SGPT elevation in mice), its congener 1,1,2-trichloroethane was much more toxic (ED_{50} = 0.1 ml/kg), and tetrachloroethylene was of equivalent potency (ED_{50} = 2.9 ml/kg).

In laboratory animals, as well as humans, the primary hazard of inhalation of high concentrations of methyl chloroform is excessive depression of the CNS. Adams et al. (1950) reported the 3-hour LC_{50} in rats to be 18,000 ppm. They observed that recovery of several test species of animals from marked depression of the CNS was rapid and uneventful. The lowest and shortest exposure that elicited histological change in tissues of the rat was 8,000 ppm for 7 hours. This treatment produced an increase in liver weight and fatty vacuolation of hepatocytes. Disturbance of vestibular function in rabbits infused intravenously with methyl chloroform was observed by Larsby et al. (1978) when blood levels exceeded 75 ppm of methyl chloroform. Also, levels of methyl chloroform in the cerebrospinal fluid were approximately one-third of that in the blood. Although this vestibular disturbance is physiologically significant, it should be noted that Gamberale and Hultengren (1973) observed inhibition of psychophysiological function in humans with blood levels of only 3-5 ppm of methyl chloroform.

A second hazard associated with acute exposure to vapor containing high concentrations of methyl chloroform is cardiovascular toxicity. The aforementioned accounts of cardiotoxic effects of methyl chloroform in humans (Bass 1970, Dornette and Jones 1960) have been confirmed in studies of dogs. Reinhardt et al. (1973) found methyl chloroform to be more potent than trichloroethylene in inducing arrhymias in dogs given epinephrine concomitantly. The lowest effective concentration of methyl chloroform was 5,000 ppm. However, Egle et al. (1976) did not detect adverse cardiovascular effect in dogs that had been exposed to 5,000 and 10,000 ppm methyl chloroform in a Freon propellant. They attributed the disparity between their own findings and those of Reinhardt et al. (1973) to differences in the experimental design. Herd et al. (1974) found methyl chloroform to exert a biphasic action on the cardiovascular system of anesthetized dogs, which was characterized by an initial decrease in blood pressure that was associated with peripheral vasodilation as well as reflex chronotropic and inotropic effects on cardiac function, and subsequent depression of cardiac function. In a study of the biochemical mechanism of methyl chloroform's cardiotoxicity, Herd and Martin (1975) observed inhibition of respiratory function and alteration of permeability characteristics in mitochondria that were isolated from rats. Herd et al. (1974) emphasized that studies are needed to determine whether low-level exposure to methyl chloroform may be injurious to the cardiovascular system.

In constrast to previous findings of microsomal enzyme induction in mice (Lal and Shah 1970) and rats (Fuller 1970) that inhaled 3,000 ppm methyl chloroform for 24 hours, inhibition of microsomal drug metabolism was observed in rats given approximately 1.4 g/kg orally (Vaino et al. 1976) and in mice 1.0 ml/kg of undiluted methyl chloroform intraperitoneally (Shah and Lal 1976). The animals were sacrificed 24 hours following administration of methyl chloroform. Shah and Lal (1976) further demonstrated that dilution of methyl chloroform with dimethylsulfoxide (DMSO) potentiated the effect, while methyl chloroform, diluted with olive oil, reduced the inhibitory effect. Shah and Lal suggested two factors that may be important are (a) the augmentation (or retardation) of absorption of chemicals by the use of different vehicles and (b) whether the chemical enters the systemic circulation directly (via inhalation) or is taken at once to the liver by way of the portal circulation (after intraperitoneal circulation).

2. Subacute Toxicity

MacEwen et al. (1974) exposed monkeys to 250 ppm and 1,000 ppm methyl chloroform for 14 weeks via inhalation. There were no significant changes in hemoglobin, red blood cell (RBC) and white blood cell (WBC) counts, Na K alkaline phosphatase, SGOT, SGPT, creatinine, chloride, glucose, blood urea nitrogen, albumin, globulin, total protein, calcium, cholesterol, total bilirubin, and serum triglycerides. Additionally, no pathological changes were detected at these concentrations.

Adams et al. (1950) exposed one female monkey to 3,000 ppm of methyl chloroform for 7 hr/day (53 exposures) over 74 days via inhalation. The monkey was necropsied and no pathological changes were found in the lungs, heart, liver, kidneys, lymph nodes, spleen, adrenals, pancreas, stomach, small and large intestines, bladder, thyroid gland, and skeletal muscles.

Prendergast et al. (1967) exposed squirrel monkeys to methyl chloroform by inhalation as follows: 2,700 ppm (8 hr/day) for 6 weeks, 450 ppm (continuously) for 90 days; and 165 ppm (continuously) for 90 days. The monkeys exposed to 2,700 ppm lost 3% of their body weight, but no microscopic pathological changes were seen, whereas the animals given 450 ppm exhibited a weight loss equalling 4% and lung inflammation. The monkeys exposed to 165 ppm gained weight but showed signs of lung congestion.

Prendergast et al. (1967) exposed beagle dogs to methyl chloroform by inhalation as follows: 2,700 ppm (8 hr/day) for 6 weeks; 450 ppm (continuously) for 90 days; and 165 ppm (continuously) for 90 days. Dogs given 2,700 ppm lost 2% of their body weight and showed blood leukopenia, but no changes in the lungs; whereas dogs exposed to 450 ppm gained weight (5% less controls) but exhibited lung inflammation. Dogs given 165 ppm gained weight normally, but showed sporadic lung congestion.

Adams et al. (1950) exposed female albino rabbits to 5,000 ppm of methyl chloroform by inhalation (7 hr/day) for a total of 44 days. The animals manifested a slight depression of growth rate but no other pathological changes were reported.

Prendergast et al. (1967) exposed guinea pigs to methyl chloroform by inhalation as follows: 2,700 ppm (8 hr/day) for

6 weeks; 450 ppm (continuously) for 90 days; and 165 ppm (continuously) for 90 days. Guinea pigs exposed to 2,700 at dose #1 were all normal. Dose #2 animals had non-specific lung inflammation, but clinical chemistry and blood were normal; dose #3 animals showed sporadic lung congestion, but, as with dose #2, clinical chemistry and blood were normal. All animals at all doses survived.

Adams et al. (1950) exposed 71 mixed strain, mixed sex, guinea pigs (roughly divided into male/female dose groups) to methyl chloroform as follows:

Dose #1:	45 days, 5,000 ppm, 7 hr/day, 5 days/week, 32 exposures
Dose #2:	29 days, 3,000 ppm, 7 hr/day, 5 days/week, 20 exposures
Dose #3:	60 days, 1,500 ppm, 7 hr/day, 5 days/week, 44 exposures
Dose #4:	92 to 93 days, 650 ppm, 7 hr/day, 5 days/week, 65 to 66 exposures
Dose #5:	57 to 58 days, 650 ppm, 7 hr/day, 5 days/week, 40 to 41 exposures

Significant decreases in growth rate occurred at all doses. Organ weights and clinical chemistry were normal at all dose levels. Microscopic pathology was normal at 1,500 ppm or less (doses #3, #4, and #5). At 5,000 ppm (dose #1), there was slight centrilobular fatty infiltration in the livers but no necrosis; slight testicular degeneration also occurred. At 3,000 ppm (dose #2), the livers showed slight centrilobular fatty infiltration, with small fat-staining globules in the central hepatocytes.

Summary

The studies discussed above present strong evidence that laboratory animals (dogs, rabbits, monkeys) under a wide variety of dosage and treatment schedules presented symptoms such as weight losses/or depressed growth rate, and lung inflammations, etc., but no pathological changes were detected at the subacute toxic levels of methyl chloroform used in the various studies. As acute toxicity levels of methyl chloroform were approached for specific animal models, hepatotoxicity increased significantly.

3. Chronic Effects

McNutt et al. (1975) exposed mice continuously to 250 and 1,000 ppm methyl chloroform for up to 14 weeks. Sacrifices were performed at weekly intervals to ascertain the development of any histopathologic abnormalities. Hepatocytic vacuolations and significant increases in liver weight and triglyceride content were observed throughout the study in animals exposed to 1,000 ppm. After weeks of exposure to 1,000 ppm methyl chloroform, a number of ultrastructural alterations were observed in centrilobular hepatocytes, including proliferation of smooth endoplasmic reticulum. Such a structural alteration would be expected in light of the reports of microsomal enzyme induction by Fuller et al. (1970) and Shah and Lal (1976). McNutt et al. (1975) saw a return to normal of each of the indices at 2 and 4 weeks after exposure. Mild or moderate ultrastructural alterations and increases in liver weight and triglycerides were occasionally observed in the animals that were exposed to 250 ppm during a 14-week study. Thus, this exposure level might be considered a threshold for a biological effect of methyl chloroform in the mouse. Platt and Cockrill (1969) studied biochemical changes in rat livers in response to a series of aliphatic halocarbons. The authors found that seven daily oral doses of 1.65 g/kg enhanced the cytoplasmic and microsomal protein content without producing any hepatotoxic effects. Savolainen et al. (1977) recently reported slight decreases in brain ribonucleic acid (RNA)and liver microsomal P-450 in rats inhaling 500 ppm of methyl chloroform (6 hours daily) for 4 or 5 days. The significance of these latter findings is uncertain.

Two lifetime feeding study that have been reported were conducted as a part of the National Cancer Institute Bioassay Program (NCI 1977, NTP draft report 1983). In an initial rangefinding study, oral doses ranging from 1,000 to 10,000 mg/kg methyl chloroform in corn oil were given to male and female mice and rats 5 days weekly for 6 weeks. The highest "noeffect" dose for rats was 3,160 mg/kg while that for mice was 5,620 mg/kg. Indices of toxicity that were evaluated included body weight and gross evidence of organ damage. A chronic dosing study was then initiated but had to be discontinued because of undefined intoxication in rats receiving 3,000 mg/kg. In the final chronic study, male and female rats received 750 or 1,500 mg/kg of methyl chloroform in corn oil by gavage five times weekly for 78 weeks. Similarly, male and female mice were given methyl chloroform doses that were increased during the study when it became apparent that larger quantities of the chemical could be tolerated. The time-weighted averages for the two dose levels in mice for the 78week regimen were approximately 2,800 and 5,600 mg/kg. Diminished body weight gain and decreased survival time were manifested in both mice and rats. Surprisingly, the incidence of histopathologic change was no greater for methyl chloroform dosed than for control animals of either species. No other indices of toxicity were evaluated.

A repeat carcinogenesis bioassay of methyl chloroform was conducted by administering the test chemical in corn oil by gavage to groups of 50 male and 50 female F344/N rats at doses of 375 and 750 mg/kg body weight. Groups of 50 male and 50 female B6C3F1 mice received 1,500 or 3,000 mg/kg body weight. Methyl chloroform was administered five times per week for 103 weeks. Groups of rats and mice of each sex received corn oil by gavage on the same schedule and served as vehicle controls.

Rats: Mean body weights for control and dosed rats were comparable throughout the two year study. There were no tumors in rats considered to be related to administration of methyl chloroform. However, the large number of accidental deaths among dosed females (25 low dose, 17 high dose) and dosed males (14 low dose, 8 high dose) reduced the sensitivity of this study for detecting late-appearing tumors in these groups. Mice: Survival of high dose male mice (28/50) was significantly ($P < 0.01$) less than that of the vehicle controls (44/50). There was a significant ($P < 0.05$) dose response trends and increased incidences of hepatocellular carcinomas in low and high dose male and in high dose female mice.

A number of long-term animal studies of the toxic potential of inhaled methyl chloroform have been conducted over the last 20 years. These studies have been directed largely towards assessing potential hazards of methyl chloroform in occupational exposure situations. Daily exposure of a variety of species to 500 ppm of methyl chloroform over a 6-month period elicited no recognizable adverse effect, but 1,000 ppm produced fatty and enlarged livers in guinea pigs (Torkelson et al. 1958). Rowe et al. (1963) reported similar findings when testing a solvent mixture consisting of approximately 75% methyl chloroform and 25% tetrachloroethylene. However, guinea pigs in the latter study did show some decrease in body weight gain, which was attributed to reduced food consumption, as well as an increase in liver weight. In studies of response to even lower concentrations, Prendergast et al. (1967) exposed rats, guinea pigs, dogs, rabbits, and monkeys to methyl chloroform vapor continuously for 90 days. They observed depressed body weight in rabbits and dogs inhaling 370 ppm, but no adverse effects in any species inhaling 135 ppm. Eben and Kimerly (1974) detected no evidence of hepatorenal injury, hematologic change, or histopathologic alteration in rats that received 200 ppm of methyl chloroform 8 hours daily (5 days a week) for 14 weeks.

Summary

Daily exposure to 500 ppm of methyl chloroform over a 6-month period elicited no recognizable adverse effects in rats, guinea pigs and other animal species. however, 1000 ppm produced fatty and enlarged livers in guinea pigs.

4. Mutagenicity

The mutagenicity of methyl chloroform has been evaluated in the B6C3F1 mouse using a host-mediated assay with *Schizosaccharomyces bombe* (Lobrien et al. 1979). The investigators have reported that methyl chloroform administered by gavage at 500 mg/kg did not increase the incidence of mutations in *S. bombe* measured after treatment following 3, 6, and 16 hours. No information was provided concerning whether or not testing was conducted to determine the ability of methyl chloroform to induce mutations *in vitro*. In addition, no data are presented concerning a determination of the toxicity of the substance to mice after acute exposure to arrive at a maximum tolerated dose for conducting the host mediated assay. Therefore, it makes it difficult to assess the significance of the results.

Two tests of the mutagenic potential of methyl chloroform in bacteria were reported to have been conducted using protocols designed to prevent evaporation of methyl chloroform and thereby ensure exposure of the indicator organisms. Both tests were reported to yield positive results (Simmon et al. 1977, Snow et al. 1979). The testing performed by Simmon and coworkers was conducted using the standard battery of *Salmonella typhimurium* strains TA 1535, TA 1537, TA 1538, TA 98, and TA 100, both with and without metabolic activation of rat liver microsome S9 fraction. The concentrations used for testing were 0, 100, 200, 300, 400, 500, 750, and 1000 ug/g - liter desiccator. A weak dose-related response was observed for TA 100 both with and without metabolic activation. The exact purity of the methyl chloroform sample tested was not given but was reported to be high.

In their studies, Snow et al. (1979) tested two samples of methyl chloroform in *Salmonella* strain TA 100 both with and without metabolic activation. Testing conducted with metabolic activation employed an S9 fraction obtained from methyl chloroform induced Syrian golden hamster liver microsomes. Similar to the study performed by Simmon et al. (1977), precautions were reported to have been taken to prevent evaporation of methyl chloroform. Doses of 0, 500, 750, 1000, and 1500 ul/5.6 liter modular incubator chamber were employed. Positive response was obtained for TA 100 to the two samples of methyl chloroform tested. One of the sample was from Aldrich (97% methyl chloroform stabilized with 3% p-dioxane) and the other was from PPG Industries (reported to be purified sample).

In a chronic inhalation study, 96 male and 96 female rats were exposed to methyl chloroform at levels of 1,750 or 875 ppm for 6 hr/day, 5 days/week, for 12 months (Quast et al. 1978). Cytogenic examination of bone marrow cells from rats sacrificed after 12 months indicated neither chromosomal damage nor chromatid aberrations in male rats. The number of scorable chromosome spreads for the female rats was very low overall; consequently data on female rats were not presented.

A test of cell transformation using the Fischer rat embryo cell line F170 was performed with methyl chloroform and other solvents. The transformed cells produced fibrosarcomas in rats when they were inoculated. The potency of the methyl chloroforminduced transformation was similar to that produced by trichloroethylene (Price et al. 1978).

Henschler et al. (1977) tested the mutagenic potential of methyl chloroform by the Ames test using Salmonella tester strain TA 100 (a highly sensitive strain). Methyl chloroform was non-mutagenic in both activated and unactivated tests.

Summary

Mutagenicity testing of methyl chloroform has proven inconclusive. The above discussion of various test systems evaluating the mutagenicity of methyl chloroform yielded the following results: 2 positive (methyl chloroform is weakly mutagenic), 3 negative, and 1 inconclusive. The inconsistent findings concerning the mutagenic potential of methyl chloroform could not be thoroughly evaluated since sufficient scientific data were not given by the various investigators in their reports. Scientific data such as: protocol design, maximum tolerated dose, purity of experimental compound, controls (negative, postive), etc. were not presented in detail.

5. Carcinogenicity

Although a variety of neoplasms were observed in methyl chloroform treated rats and mice and their respective controls, no positive correlation relationship was found between treatment and incidence of neoplasm. The shortened lifespans of the rats and mice made an assessment of ingested methyl chloroform carcinogenicity impossible (National Cancer Insititute 1977).

In the earlier studies, rats of the Osborne-Mendel strain and B6C3F1 mice (50 of each sex of each rodent) were given methyl chloroform orally in corn oil at each of two dose levels 5 days/week for 78 weeks.

Rats on chronic studies received high and low doses of 1,500 or 750 mg/kg; mice received adjusted doses averaging 5,615 or 2,807 mg/kg. The methyl chloroform used in the carcinogenicity studies was technical grade. Male and female weanlings were started on the test at 5 weeks of age and sacrificed at 96 weeks of age. Initially, the doses for male and female mice were 4,000 and 2,000 mg/kg body weight. During the 10th week of the study, doses were increased to 5,000 and 2,500 mg/kg. During the 20th week of the study, doses were again increased to 6,000 and 2,000 mg/kg and maintained at these levels to the end of the study.

At death, all animals were necropsied except those in which autolysis had occurred. Approximately 29 different tissues were fixed informalin, sechoned, stained, and examined microscopically. Comparison of the numbers and distribution of lesions in treated and control groups revealed no excess of histopathological lesions that could be related to treatment.

The median survival of all groups except the female control mice was lower than would normally be expected. This may be due, in part, to the chronic murine pneumonia which was prevalent and was the most probable cause for the high incidence of natural deaths.

In the repeat NTP bioassay study (draft report 1983), Fischer 344/N rats and B6C3F1 mice were gavaged with daily doses of 375 or 750 mg/kg body weight (rats) and 1,500 or 3,000 mg/kg body weight of methyl chloroform in corn oil, respectively. The compound was administered to groups of 50 rats and 50 mice (each sex) five times per week for 103 weeks. There was no change in mean body weights for control and dosed rats, however, mean body weights of dosed male and female mice were slightly lower than those of the vehicle controls. No methyl chloroform related tumors were observed in rats, but the large number of accidental deaths among dosed females (25 low dose; 17 high dose) and dosed males (14 low dose; 8 high dose) reduced the sensitivity of this study for detecting late-appearing tumors in those groups.

In mice, (NCI 1983), there was an increase in hepatocellular carcinomas occurrence in low and high dosed male and in high dosed female mice: males - vehicle control 16/50, low dose 24/50, high dose 20/50; females - vehicle control 3/49, low dose 5/49, high dose 10/49. NCI concluded that: (1) methyl chloroform was not carcinogenic for male F344/N rats (2) the study was considered inadequate for carcinogenesis evaluation in female F344/N rats, (3) the association between the administration of methyl chloroform and the increased incidences of hepatocellular carcinomas in male B6C3fl mice was considered equivocal, and (4) methyl chloroform was carcinogenic for female B6C3Fl mice, causing an increased incidence of hepatocellular carcinomas.

Price et al. (1978) demonstrated the *in vitro* transforming potential of methyl chloroform (99.9 percent pure) using the Fischer rat embryo cell system (F1706). Rat embryo cell cultures were treated with methyl chloroform, diluted in growth medium, for 48 hours. After nine subcultures, the transformed cells (characterized by morphology and formation of macroscopic foci in semi-soft agar) were inoculated into newborn Fischer rats. After 68 days, the transformed cells had grown as undifferentiated fibrosarcomas at the inoculation sites in all tested animals. Acetone, the negative control, did not induce tumors after 82 days of inoculation (Price et al. 1978).

Summary

In the repeat NTP bioassay in rats and mice, there was an increase in hepatocellular carcinomas occurrence in low and high dose males and high dose females. NTP concluded that (1) methyl chloroform was not carcinogenic for male rats, (2) the study was considered inadequate for carcinogenesis evaluation in female rats, (3) the association between the administration of methyl chloroform and the increased incidences of hepatocellular carcinomas in male mice was considered equivocal, and

(4) methyl chloroform was carcinogenic for female mice, causing an increased incidence of hepatocellular carcinomas. However, it should be noted that the NTP repeat bioassay is undergoing audit, and that these findings of audit may change the above conclusion when the audit report is published.

6. Teratogenicity

Schwetz et al. (1975) assayed for reproductive and teratogenic effects in Sprague-Dawley rats (250 g) and Swiss Webster mice (25 to 30 g) exposed to 875 ppm of methyl chloroform by inhalation for 7 hr/day from gestation day 6 to gestation day 15. The compound was a commercial grade preparation and contained 5.5% or about 50 ppm inhibitors. Caesarian sections were performed on gestation day 21 (rats) and 18 (mice). Livers in treated maternal rats were heavier than those in the controls ($p < 0.05$), but no significant changes in hepatic weights were reported in mice. No teratogenic effects were seen in all exposed rats and mice for the following parameters: weight gain; percent fetal resorptions; average litter size; fetal body measurements; fetal gross anomalies; skeletal anomalies; microscopic examination and maternal carboxyhemoglobin content.

Lane et al. (1982) studied the effects of methyl chloroform in drinking water on teratogenicity and reproduction in mice. Male and female ICR Swiss mice received methyl chloroform at concentrations of 0, 0.58, 1.75 or 5.83 mg/ml. These concentrations were designed to yield daily methyl chloroform doses of 0, 100, 300 or 1,000 mg/kg. The investigators stated that: (1) there appeared to be no dose-dependent effects on fertility, gestation, viability, or lactation indices, (2) pup survival and weight gain were not adversely affected, and (3) methyl chloroform failed to produce significant dominant lethal mutations or terata in either of the two generations tested.

Summary

Rats and mice have been studied for the teratogenic potential of methyl chloroform. No effects were evident in exposed animals for the following parameters: weight gain, percentage fetal reabsorption, average litter size, fetal body measurements, gross skeletal anomalies, and maternal carboxyhemoglobin content. There are some indications that mating and fertility indices of exposed animals were lower, and some abnormalities appeared, but were not statistically significant. Thus, methyl chloroform-induced teratogenicity has not been established.

VI. HEALTH EFFECTS IN HUMANS

1. Acute Toxicity

The primary toxic effects of short-term, high-level exposure to methyl chloroform in humans are characterized by depression of the CNS. In the majority of reports of human fatalities resulting from methyl chloroform inhalation, death is attributed to a functional depression of the CNS. Levels of methyl chloroform in the victims' blood varied considerably, ranging from 60 (Hatfield and Maykoski 1970, Stahl et al. 1969) to 720 ppm (Hall and Hine 1966). The highest concentrations of methyl chloroform were found in the brains of victims (Caplan et al. 1976, Stahl et al. 1969). Due to problems that are inherent in analyses of volatile toxicants in autopsy samples, it is difficult to establish lethal methyl chloroform concentrations in blood or tissues.

Inhalation of high concentrations of methyl chloroform can cause irritation of the respiratory tract and minimal organ damage, as well as depression of the CNS. Acute pulmonary congestion, an edema typically found in fatalities result from inhalation of methyl chloroform (Bonventre et al. 1977, Caplan et al. 1976). There are also scattered reports of modest fatty vacuolation in the liver (Caplan et al. 1976, Hall and Hine, 1966, Stahl et al. 1969). In most such instances, there probably would have been insufficient time between exposure and death for hepatotoxicity to be fully expressed. Stewart (1971) reported the case histories of four individuals who were monitored clinically after being overcome by methyl chloroform vapors. In each case, recovery from depression of the central nervous system was quite rapid and largely uneventful. However, one of the four patients exhibited elevated urinary urobilinogen but no alteration of other indices of hepatotoxicity. These studies indicate that methyl chloroform possesses a limited capacity to exert hepatic injury in cases of acute, high-level inhalation exposure.

Clinical experience and scientific investigations suggest that acute high-level inhalation of methyl chloroform can adversely affect the cardiovascular system of humans. Dornette and Jones (1960) used concentrations of 10,000-26,000 ppm methyl chloroform to anesthetize surgery patients. They noted that both induction of and recovery from anesthesia were quite rapid. No evidence of respiratory depression or hepatotoxicity was seen. However, there were disturbing cardiovascular effects including diminished systolic pressure, premature ventricular contractions, and, in one patient, even cardiac arrest. Positive urinary urobilinogen was found ranging from 7 hours to 20 hours after exposure.

Bass (1970) reported a syndrome called "sudden sniffing death" in persons dying abruptly while inhaling volatile solvents for self-intoxication. Methyl chloroform was one of the most suspect solvents in such incidents. The fatalities were attributed to cardiac arrhythmias that resulted from a combined action of the solvent and endogenous biogenic amines.

A single account of methyl chloroform ingestion by a human has appeared in the literature (Stewart and Andrews 1966). A 47-year-old male mistakenly drank 1 oz. of methyl chloroform (approximately 0.6 g/kg). He became nauseated within 30 minutes and developed progressively severe vomiting and diarrhea over the next few hours. Urinalysis and clinical chemistry tests revealed evidence of only minimal hepatorenal injury early in the course of hospitalization. After treating the vomiting and diarrhea symptoms, the patient was asymptomatic during a 2-week observation period.

Since depression of the CNS is the predominant effect of methyl chloroform on humans, certain manifestations of the depression should be the most sensitive index of the pathophysiological action of small quantities of the solvent. Early studies with volunteers indicate that inhalation of 500 ppm of methyl chloroform for several hours has no significant effect other than transient, mild eye irritation (Stewart et al. 1961 Torkelson et al. 1958). Stewart and his co-workers (1969) concluded in a later study that 500 ppm of the chemical may be excessive for persons who are particularly susceptible to the chemical's depressant effects on the CNS. In a recent investigation, inhalation of 350 ppm of methyl chloroform for 4 hours was not effective, whereas 450 ppm elicited subjective complaints of transient eye irritation and dizziness (Salvini et al. 1971). Although a number of psychophysiological tests did not reveal a statistically significant degree of functional inhibition, lower scores resulted when tests were conducted during methyl chloroform exposure than when under control conditions. Results of an investigation by Gamberale and Hultengren (1973) indicated that inhalation of 350 ppm of methyl chloroform can significantly inhibit psychophysiological functions in humans. Five performance tests were used, 2 were tests of perceptual speed and the others were tests of simple reaction time, choice reaction time, and manual desterity. Blood levels in the "inhibited" subjects averaged approximately 3-4 ppm, although the investigators noted wide intersubject differences in blood and alveolar air concentrations. Gamberale and Hultengren concluded that it would be difficult, with any degree of accuracy, to set a threshold for the vapor concentration of methyl chloroform that would not alter function of the central nervous system. Their tests of psychophysiological function are certainly more sensitive and objective than the indices used in the earlier studies of Torkelson et al. (1958) and Stewart et al. (1961, 1969). Nevertheless, the current U.S. threshold limit value for occupational exposure to methyl chloroform remains at 350 ppm. This standard is designed to protect the majority of workers from mucous membrane irritation and performance inhibition.

2. Subacute Toxicity

Short-term exposure to methyl chloroform appears to be no more harmful to humans or laboratory animals than does acute exposure. Stewart et al. (1969) exposed humans via inhalation to 500 ppm methyl chloroform for 6.5 hours daily for five consecutive days. They observed some objective and subjective signs of depression of the central nervous system, but no evidence of toxicity upon examination for neurological, respiratory, and hepatorenal function. There were also a small accumulation of methyl chloroform and an increase in urinary trichloroethanol levels.

3. Epidemiology

Seki and his colleagues (1975) surveyed four Japanese printing factories where methyl chloroform, the sole organic solvent in the entire process, was used to remove excess ink. Duration of workday/workweek and operational procedures were essentially uniform. Enclosure of vapor sources and installation of exhaust systems were, in the authors' opinion, mainly responsible for variation in vapor concentration. The subjects were 23-53 year-old men and had been exposed to methyl chloroform vapor for at least 5 years. Laboratory tests, including peripheral hemograms, blood specific gravity and urinalysis for urobilinogen and protein, were not described. A Japanese version of the Cornell Medical Index health questionnaire was answered by all subjects. A test of vibrational sense was performed as well as urinalysis for trichloracetic acid and methyl chloroform. Decrease in urinary metabolite levels provided the basis for calculation of biologic half-life. The vapor concentration of methyl chloroform in the workroom air was determined by gas-liquid chromotography. A preliminary study revealed a fairly constant vapor concentration regardless of time and location of sampling. The respective data are presented in Tables VI-1, VI-2, and VI-3.

The authors found, through regression analysis, a linear relationship between the vapor concentration of methyl chloroform and level of urinary metabolites (trichloroacetic acid and methyl chloroform), and for this reason they concluded that the urinary metabolite level was a good index of methyl chloroform exposure. The biological half-life of methyl chloroform was found to be 8.7 ± 1.8 hours.

In a detailed study of one worker, a steady increase in urinary metabolite concentrations toward the weekend as well as significant metabolite excretion on Sunday, suggested that methyl chloroform accumulated in the body. Total metabolite increase was primarily attributed to methyl chloroform.

No dose-dependent difference in health, as reflected by the medical questionnaire, was found in any of the workers. The authors recommended, based on accumulation of methyl chloroform.

TABLE VI-1 Urinary Metabolite Concentration in Workers Exposed to Methyl Chloroform

Exposure Concentration (ppm)	Metabolite Concentration (mg/l)*		No. Examined
	Trichloroacetic acid	Trichloroethanol	
4	0.6 (0.5-1.1)	1.2 (0.5-2.6)	10
25	2.4 (1.3-4.6)	5.5 (3.6-8.6)	26
53	3.6 (2.4-5.5)	9.9 (6.8-14.5)	10

* Geometric mean with SD in parenthesis.

Adapted from Seki et al. (1975).

TABLE VI-2 Results of Physical Examinations of Workers Exposed to Methyl Chloroform

Exposure Concentration (ppm)	No. Examined	No. of Healthy Subjects*	Percentage
4	66	60	91
25	33	30	91
28	55	48	87
53	42	36	86

* Adapted from Seki et al. (1975).

TABLE VI-3 Exclusions from Healthy Category By Class of Disorder

Class of Disorder	No.	Percent Affected
Cardiovascular	10	5
Hepatic	3	1
Gastrointestinal	4	2
Renal	2	1
Bone	1	<1
CNS	1	<1

Adapted from Seki et al. (1975)

in the body, a subtraction from the maximum "no adverse effect" level for short-term exposures to establish a threshold limit value (TLV) for repeated exposures (Seki et al. 1975). The odor threshold has been reported to be as high as 700 ppm or as low as 16 ppm.

Hervin (1975) determined that the total daily exposure to methyl chloroform was not at a personally hazardous level after an evaluation of 35 employees in a textile dye plant. Breath and area air were sampled and the highest level found was 220 mg/^{3} (40.5 ppm) in a 1.3-liter breath sample.

Giles and Rostand (1975) measured air levels, interviewed 15 employees, and studied the plant insurance records in another evaluation of an industrial site. The breathing zone and area samples obtained were 7-18 ppm and 14 ppm, respectively. No hazard was seen with this exposure. NIOSH has investigated additional workplace sites to evaluate worker exposure to methyl chloroform and adverse action. Methyl chloroform levels were below those allowed in the workplace (Giles and Philbim 1978, Markel 1978, Gilles 1977).

Maroni et al. (1977) studied 29 women working at a factory manufacturing platinic and steel spinerets. Twenty-two of the women were exposed to methyl chloroform in a workplace where it was the only solvent used. Seven were employed in the same factory with no known exposure to methyl chloroform. Air concentrations in the exposed areas ranged from 110 to 990 ppm with only one worker in the area with the higher concentrations (720-990 ppm). Women were subdivided into three groups according to extent of exposure: I (7 workers) 110 ppm, II (7 workers) 140-160 ppm, and III (8 workers) 990 ppm. The mean length of employment was 6 years.

No significant differences were observed between the exposed and unexposed females with respect to clinical features, maximal motor conduction velocity, conduction velocity of slow fibers and psychometric data. However, since the study group was so small and had a wide range in age, and the methods of data collection may not have been adequately standardized, the negative results of this study may not be conclusive and do not provide information on the population risks associated with exposure to methyl chloroform.

Kramer et al. (1978) conducted a study of textile workers at a plant using methyl chloroform and compared them with a group of workers at an adjacent plant not using methyl chloroform matched by age (5 years), race, sex, job description, shift, and socio-economic status. Most exposures were from 1 to 5 years at time weighted average levels of 100-250 ppm, determined from work histories and industrials hygiene surveys. The methyl chloroform contained 4% stabilizers; small quantities of fluorocarbon 113 were used in 1973. Primary emphasis was on cardiovascular effects via nurse administered questionnaires, blood parameters including enzyme assays, blood pressures, and electrocardiograms. No evidence of adverse effects on the cardiovascular system, CNS, or liver was found in this study.

The limitations of this study in terms of design, duration of exposure, and non-specificity of endpoint variables make the results difficult to apply to determinations of risk of exposure to methyl chloroform.

Summary

Transient eye irritation and upper respiratory irritation from exposure to methyl chloroform vapors have been reported at concentrations in excess of 500 ppm. Regression analysis has indicated a linear relationship between vapor concentration of methyl chloroform and the levels of urinary metabolites (trichloroacetic acid and methyl chloroform). The odor threshold of methyl chloroform covered a wide range (16-700 ppm) indicating that individual sensitivity may play a part in determining irritation and other health effects.

VII. HUMAN RISK ASSESSMENT

1. Current Levels of Exposure

Exstimates of human exposure to chloroethanes via ingestion are not available. NIOSH (1978) estimated that of over five million workers exposed to chloroethanes by inhalation and dermally.

Workers, who are occupationally exposed to chloroethanes, by inhalation and/or dermally represent a special group at risk. Epidemiological studies have not disclosed a relationship between exposure to chloroethanes and cancer; however, four chloroethanes have proved to be carcinogenic in at least one species of rodent (NCI 1978). Those individuals who are exposed to known hepatotoxins or have liver disease may constitute a group at risk.

2. Existing Guidelines and Standards

OSHA standards and NIOSH recommended standards are based on exposure by inhalation (Table VII-2).

The CAG and NAS have not calculated the projected excess cancer risk resulting from lifetime exposure to methyl chloroform. CAG is currently evaluating the technical findings of NCI bioassay in animals for denvanhonol risk.

Table VII-1 Chloroethane Exposures and Produciton

Chemical	Estimated number of workers exposed	Annual Production quantities (pounds)
monochloroethane	113,000	670 million (1976)
1,1-dichloroethane	4,600	b
1,2-dichloroethane	1,900,000	8 billion (1976)
methyl chloroform	2,900,000	630 million (1976)
1,1,2-trichloroethane	112,000	c
1,1,1,2-tetrachloroethane	a	b
1,1,2,2-tetrachloroethane	11,000	c
pentachloroethane	a	b
hexachloroethane	1,500	b,d

[a] NIOSH estimates not available.
[b] Does not appear to be commercially produced in the United States.
[c] Direct production information not available.
[d] 730,000 kg were imported in 1976.

Adapted from NIOSH (1978).

Table VII-2 Chloroethane Exposure Standards

Chemical	OSHA Exposure Standard (ppm)
monochloroethane	1,000
1,1-dichloroethane	100
1,2-dichloroethane	50
methyl chloroform	350
1,1,2-trichloroethane	10
1,1,1,2-tetrachloroethane	none
1,1,2,2-tetrachloroethane	5
pentachloroethane	none
hexachloroethane	1

*NIOSH has tentative plans for a Criteria Document for a Recommended Standard for this substance.

Adapted from NIOSH (1978).

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VIII. Quantification of Toxicological Effects

The quantification of toxicological effects of a chemical consists of an assessment of the non-carcinogenic and carcinogenic effects. In the quantification of non-carcinogenic effects, an Adjusted Acceptable Daily Intake (AADI) for the chemical is determined. For ingestion data, this approach is illustrated as follows:

$$\text{Adjusted ADI} = \frac{(\text{NOAEL or MEL in mg/kg})(70\ \text{kg})}{(\text{Uncertainty factor})(2\ \text{liters/day})}$$

The 70 kg adult consuming 2 liters of water per day is used as the basis for the calculations. A "no-observed-adverse-effect-level" or a "minimal-effect-level" is determined from animal toxicity data or human effects data. This level is divided by an uncertainty factor because, for these numbers which are derived from animal studies, there is no universally acceptable quantitative method to extrapolate from animals to humans, and the possibility must be considered that humans are more sensitive to the toxic effects of chemicals than are animals. For human toxicity data, an uncertainty factor is used to account for the heterogeneity of the human population in which persons exhibit differing sensitivity to toxins. The guidelines set forth by the National Academy of Sciences (Drinking Water and Health, Vol. 1, 1977) are used in establishing uncertainty factors. These guidelines are as follows: an uncertainty factor of 10 is used if there exist valid experimental results on ingestion by humans, an uncertainty factor of 100 is used if there exist valid results on long-term feeding studies on experimental animals, and an uncertainty factor of 1000 is used if only limited data are available.

In the quantification of carcinogenic effects, mathematical models are used to calculate the estimated excess cancer risks associated with the consumption of a chemical through the drinking water. EPA's Carcinogen Assessment Group has used the multistage model, which is linear at low doses and does not exhibit a threshold, to extrapolate from high dose animal studies to low doses of the chemical expected in the environment. This model estimates the upper bound (95% confidence limit) of the incremental excess cancer rate that would be projected at a specific exposure level for a 70 kg adult, consuming 2 liters of water per day, over a 70 year lifespan. Excess cancer risk rates also can be estimated using other models such as the one-hit model, the Weibull model, the logit model and the probit model. Current understanding of the biological mechanisms involved in cancer do not allow for choosing among the models. The estimates of incremental risks associated with exposure to low doses of potential carcinogens can differ by several orders of magnitude when these models are applied. The linear, non-threshold multi-stage model often gives one of the highest risk estimates per dose and thus would usually be the one most consistent with a regulatory philosophy which would avoid underestimating potential risk.

The scientific data base, which is used to support the estimating of risk rate levels as well as other scientific endeavors, has an inherent uncertainty. In addition, in many areas, there exists only limited knowledge concerning the health effects of contaminants at levels found in drinking water. Thus, the dose-response data gathered at high levels of exposure are used for extrapolation to estimate responses at levels of exposure nearer to the range in which a standard might be set. In most cases, data exist only for animals; thus, uncertainty exists when the data are extrapolated to humans. When estimating risk rate levels, several other areas of uncertainty exist such as the effect of age, sex, species and target organ of the test animals used in the experiment, as well as the exposure mode and dosing rates. Additional uncertainty exists when there is exposure to more than one contaminant due to the lack of information about possible additive, synergistic or antagonistic interactions.

A. Non-carcinogenic Effects

The toxic effects of 1,1,1-trichloroethane (methyl chloroform) in animals and humans following acute and chronic exposure at high doses are (1) fatty vacuolation and increase in liver weight; (2) manifestations of depression of the central nervous system; (3) transient eye irritation and dizziness; and (4) cardiovascular changes including increase in systolic pressure and premature ventricular contractions.

Effects of acute exposure to methyl chloroform in rats were reported by Adams et al. (1950). The investigators stated that the 3-hour LC_{50} in rats was 18,000 ppm. The lowest and shortest exposure that elicited histological change in tissues of rats was 8,000 ppm for 7 hours. This produced an increase in liver weight and fatty vacuolation of hepatocytes.

McNutt et al. (1975) exposed mice continuously (inhalation) to 250 and 1,000 ppm methyl chloroform for 14 weeks. Control mice were exposed to room air. Serial sacrifice of exposed and control mice from 1 to 14 weeks demonstrated significant changes in the centrilobular hepatocytes of animals in the 1000 ppm group. There was also an evidence of liver triglyceride accumulation in the 1000 ppm. Findings are summarized in Table VIII-1.

Electron microscopic evaluation of mice liver in the above study (McNutt et al. 1975) revealed that cytoplasmic alterations were most severe in centrilobular hepatocytes in the 1000 ppm group and were mild to minimal in the 250 ppm group. These alterations consisted of vesiculation of the rough endoplasmic reticulum, with loss of attached polyribosomes, increased smooth endoplasmic reticulum, microbodies, and triglyceride

Table VIII-1 Summary of Effects in Mice After Continuous Inhalation Exposure to Methyl Chloroform[a]

Parameter	250 ppm	1,000 ppm
Food/water intake	Not significantly different from control	Not significantly different from control
Liver wt/100 gm. b.w.	Not significantly different from control except at 8 and 9 week intervals	Significantly different from control
Light microscopic observation:		
Lipid contents	Significantly different at 13-week interval	Significantly different at 2-14 week intervals
Electron microscopic observations:		
Cytoplasmic alterations[b]	Mild to minimum in centrilobular hepatocytes	Severe in centrilobular hepatocytes necrotic hepatocytes (associated with focal infiltrates of neutrophilic leukocytes in the hepatic lobules)

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[a] Adapted from McNutt et al. (1975) Lab. Invest. 32:642-654.

[b] Alteration consisted of: (i) vesiculation of the rough endoplasmic reticulum, (ii) loss of attached polyribosomes and (iii) increased smooth endoplasmic reticulum microbodies

droplets. There was also present necrosis of individual hepatocytes which was associated with an acute inflammatory infiltrate and hypertrophy of Kupfler cells. The investigators stated that the comparison of these findings to the results obtained by other investigators studying with methyl chloroform were similar to those observed with dichloromethane.

Exposure to 500 ppm (7 hours/day, 5 days/week for 6 months) produced no effect on rats (#20), guinea pigs (#8), rabbits (#2) and monkeys (#2), when compared with controls in terms of growth, organ weights, hematologic values, gross pathology and histopathology (Torkelson et al. 1958). The investigators reported that female guinea pigs which were found to be the most sensitive in previous experiments were able to tolerate 1,000 ppm for 0.6 hours/day with no detectable adverse effects. Male rats tolerated exposure of 0.5 hours/day to 10,000 ppm with no organic injury.

Epidemiological evidence cannot be related to the exposure levels of methyl chloroform with confidence; however, exposures of workers to methyl chloroform and its association with observed health effects - fatigue, dizziness, nervous system disorders, etc. is worth mentioning.

Two lifetime feeding or gavage studies have been conducted as a part of the National Cancer Institute (NCI) Bioassay Program (1977, 1983). In the first study, male and female rats were given 750 or 1,500 mg/kg methyl chloroform in corn oil by gavage 5 times weekly for 78 weeks. Similarly, male and female mice received approximately 2,800 and 5,600 mg/kg for 78 weeks. Diminished body weight gain and decreased survival time were manifest in both rats and mice. The incidence of histopathological change was no greater for methyl chloroform than for control animals of either species. No other indices of toxicity were evaluated.

In the second NTP bioassay study (draft report 1983), Fischer 344/N rats and B6C3Fl mice were gavaged with daily doses of 375 or 750 mg/kg body weight (rats) and 1,500 or 3,000 mg/kg body weight (mice) of methyl chloroform in corn oil, respectively. The compound was administered fives times per week for 103 weeks. The report stated that: (1) methyl chloroform was not considered tumorgenic for male rats and this study was inadequate for tumorigenic evaluation in female rats because of the large number of accidental deaths and because of the high dose being toxic; (2) the association between the administration of methyl chloroform and the increased incidences of tumors in male B6C3Fl mice was considered equivocal, whereas there was a significant increase in tumor incidence in female B6C3Fl mice.

Lane et al. (1982) have reported results of methyl chloroform in drinking water on reproduction and development in mice. A multi-generation reproduction study was carried out in mice in addition to screening for dominant lethal and teratogenic effect of methyl chloroform. Male and female Swiss mice received methyl chloroform at concentrations of 0, 0.58, 1.75 or 5.83 mg/ml to yield daily doses of 0, 100, 300, or 1,000 mg/kg. There appeared to be no dose-dependent effects on fertility, gestation, viability, or location indices. Pup survival and weight gain were not adversely affected. Methyl chloroform also failed to produce significant dominant lethal mutations or terata in either of the two generations tested. The results of these studies could not be used in the development of a QTEL because animals were maintained only for 35 days on test solution containing specified concentrations of methyl chloroform and also the study did not identify a dose-response level at which an effect occurred.

Synergistic/additive effects and other related effects such as resulting from multiple chemical exposure with respect to methyl chloroform have not been studied in either in vitro or in vivo systems.

B. Quantification of Non-carcinogenic Effects

The liver of the mammalian system appears to be the sensitive endpoints with respect to the adverse health effects. There are limited data concerning the dosage, duration of exposure and the effects on the central nervous system.

Liver toxicity should be considered as an endpoint for estimating Adjusted Acceptable Daily Intake (AADI) for methyl chloroform. The compound has been shown to cause hepatocytic vacuolation and increase in liver weight and triglyceride content in animals. In the absence of definitive information on the chronic toxicity of ingested methyl chloroform, NAS (1980) had calculated the chronic Suggested No Adverse Response Level (SNARL), 3.8 mg/1, based on the lowest dose used in the NCI bioassay (1977) in animals. Similarly, U.S. EPA (AWQD, 1980) and (ODW) have also considered the lowest dose of 750 mg/kg of methyl chloroform administered orally in calculating ADI and Health Advisories, respectively. These levels are shown in Table VIII-2. However, in view of recent findings of NCI bioassay in rats and mice and lack of chronic ingestion studies of methyl chloroform in animals for quantifying non-carcinogenic effect, it may be prudent to consider inhalation study in animals (McNutt et al. 1975), in addition to data of repeat NCI bioassay (1983) even though the inhalation studies in animals may not meet all criteria necessary for quantifying non-carcinogenic effects.

McNutt et al. (1975) exposed male mice continuously (inhalation) to 250 (1,365 mg/m^3) or 1,000 ppm (5,460 mg/m^3) methyl chloroform for 14 weeks. Control mice were exposed to room air. Serial sacrifice of exposed and control mice from 1 to 14 weeks demonstrated significant changes in the centrilobular hepatocytes of animals in the 1,000 ppm (5,460

Table VIII-2 Health Advisory for Methyl Chloroform

	NAS-SNARL	EPA-HA	AWQD-ADI	WHO
Non-CA	3.8 mg/l[a]	1.07 mg/l[b]	18.7 mg/l[c]	-
CA	-	-	-	-

NOTE:
- Not available.

[a] Based on NCI bioassay study in rats - 750 mg/kg (NCI 1977) and ≠ is calculated for an adult weighing 70 kg consuming 2 liters of water and contribution from water being 20% (NAS 1980).

[b] Based on NCI bioassay study in rats - 750 mg/kg (NCI 1977) and is calculated for a 10 kg child consuming 1 liter of water and contribution from water being 20% (USEPA Health Advisory 1980).

[c] Based on NCI bioassay study in rats - 750 mg/kg (NCI 1977) and is calculated for an adult weighing 70 kg consuming 2 liters of water and assuming 100% of exposure from water (USEPA - AWQD 1981).

mg/m^3) group and mild to minimal in the 250 ppm (1,365 mg/m^3) group. These changes consisted of vesiculation of the rough endoplasmic reticulum, with loss of attached polyribosomes, increased smooth endoplasmic reticulum, microbodies, and triglyceride droplets. No no-observed-adverse-effect-level (NOAEL) can be identified but a MEL (Minimum Effect Level) of 250 ppm (1,365 mg/m^3) can be used. An ADI based upon these data could be derived as follows:

$$\frac{(1365\ \text{mg/m}^3)(1\ \text{m}^3/\text{hr})(6\ \text{hrs})(0.30)}{(1000)\ (2\ 1/\text{d})} = 1.2\ \text{mg/1} = 1.0\ \text{mg/1}$$

(or 0.014 mg/kg/day
for a 70 kg adult)

where

1,365 mg/m^3 (250 ppm) = MEL
1 m^3/hr = Ventilation volume for a 70 kg adult
6 hrs = Exposure assumed to be saturable and therefore equivalent to exposure for 24-hour period
0.30 = Absorption factor
1000 = Uncertainty factor appropriate to MEL in animals with no equivalent data in the human
70 kg = Average body weight of an adult
2 1/day = Water consumption per day for an adult

Strength: Serial sacrifice of exposed mice from 1 to 14 weeks demonstrated significant changes in the centrilobular hepatocytes of animals.

Weakness: (1) Route of exposure is inhalation and the period of continuous exposure was for 98 days. (2) Percent body burden of methyl chloroform following 24-hr continuous exposure is not available. (Calculations are based on 6-hr inhalation exposure results.)

NCI repeat ingestion study in rats

Methyl chloroform was administered in corn oil by gavage to groups of 50 male and 50 female rats (F344/N) at doses of 375 and 750 mg/kg body weight. Methyl chloroform was given 5 times per week for 103 weeks.

No biologically significant tumor pathology was observed in these rats. The increase in intestinal cell testicular tumors was not considered to be related to the administration of methyl chloroform in the high dose group. However, the survival of high dose female rats in the present study was significantly less ($P < 0.001$) than that of the vehicle control. A large number of accidental deaths due to gavage errors occurred among dosed female and male rats (25 low dose and 17 high dose females and 14 low dose and 8 high dose males). An ADI based upon low dose, 375 mg/kg, may be derived as follows:

$$\frac{(375\ \text{mg/kg})(5\ \text{days})(70\ \text{kg})}{(7\ \text{days})(2\ \text{1/day})(1{,}000)} = 9.38\ \text{mg/1} = 9.4\ \text{mg/1}$$

where

375 mg/kg = observed adverse effect dose
5/7 = fraction converting from 5 to 7 day exposure
70 kg = average weight of an adult

1000 = uncertainty factor

2 1/day = adult consumption of water per day

Strength: The exposure is via ingestion and for a lifetime (103 weeks).

Weakness: This study suffers from one important criteria and that is poor survival of animals at the end of 103 weeks of exposure. A large number of deaths in animals occurred over the 103 weeks of exposure either due to gavage error or to the toxicity of methyl chloroform administration in high dose groups of animals. The survival rate for animals at the end of the 103 week exposure is shown below:

Survival of Animals

Animal	Control 0	Low Dose 375 mg/kg	High Dose 750 mg/kg
Female	29/50	10/50	5/50
Male	36/50	20/50	26/50

Since no methyl chloroform effects were observed in the repeat NCI bioassay in rats, the ingestion dose level of 375 mg/kg would have been appropriate for the derivation of an ADI. However, the repeat study in rats suffers from the high death rate either from gavage error or toxic effects of methyl chloroform (in high doses) in animals. The percent deaths in the female rats at end of the 103 week period were 42%, 80%, and 90% in the control, low dose (375 mg/kg), and high dose (750 mg/kg), respectively. Therefore use of this study in the derivation of an ADI is highly questionable for methyl chloroform. Therefore, in view of the above observation and lack of other chronic ingestion studies of methyl chloroform in animals for quantifying non-carcinogenic effect, it may be prudent to consider inhalation data in animals (McNutt et al. 1975), even though this inhalation study in mice may not meet all criteria necessary for quantifying non-carcinogenic effects (such as short period of exposure, route of exposure other than ingestion, inadequate information on body burden from 24 hour continuous exposure).

Under the circumstances, the adjusted ADI for methyl chloroform, 1.0 mg/1, using non-carcinogenic inhalation data and 100% exposure from drinking water is tentatively identified.

C. Carcinogenic Effects

Two animal bioassays by NCI have been completed in F344 rats and B6C3Fl mice. In the earlier NCI bioassay, Osborne-Mendel rats (750 mg/kg and 1,500 mg/kg) and B6C3Fl mice (2,800 mg/kg and 5,615 mg/kg) were treated with methyl chloroform in corn oil 5 times a week for 78 weeks by gavage (NCI 1977). Rats were observed an additional 32 weeks and mice another 12 weeks. The study was inadequate because only 3% of the treated rats survived to the end of the experiment. A variety of neoplasms were observed in methyl chloroform treated and matched-control animals. The neoplasms observed were not believed attributable to methyl chloroform exposure since no relationship was established between the dosage groups, species, sex, type of neoplasm, or site of occurrence. It was concluded that the carcinogenicity could not be determined from this study (NCI 1977).

A repeat carcinogenesis bioassay of methyl chloroform was conducted by administering the test chemical in corn oil by gavage to groups of 50 male and 50 female F344/N rats at doses of 375 and 750 mg/kg body weight. Groups of 50 male and 50 female B6C3F1 mice received 1,500 or 3,000 mg/kg body weight. Methyl chloroform was administered five times per week for 103 weeks. Groups of rats and mice of each sex received corn oil by gavage on the same schedule and served as vehicle controls. Rats: Mean body weights for control and dosed rats were comparable throughout the two year study. There were no tumors in rats considered to be related to administration of methyl chloroform. However, the large number of accidental deaths among dosed females (25 low dose, 17 high dose) and dosed males (14 low dose, 8 high dose) reduced the sensitivity of this study for detecting late-appearing tumors in these groups. Mice: Survival of high dose male mice (28/50) was significantly ($P < 0.01$) less than that of the vehicle controls (44/50). There was a significant ($P < 0.05$) dose response trend and increased incidences of hepatocellular carcinomas in low and high dose male and in high dose female mice.

Dow Chemical Co. (Quast et al. 1978) studied groups of Sprague-Dawley rats exposed by inhalation (6 hours/day, 5 days/week, over one-half of a lifetime). Rats were treated for 12 months and observed until death or until they reached the age of 31 months. The dose of 875 and 1,750 ppm were 2.5 and 5 times the threshold limit value of 350 ppm, respectively. There are two shortcomings of this study: 1) the animals were treated for only 12 months rather than a lifetime but observed for another 12 months, and (2) it is not evident that the maximum tolerated dose was used during the treatment period. The only sign of toxicity was an increased incidence of focal hepatocellular alterations in female rats at the highest dosage.

Methyl chloroform has been tested for its ability to cause point mutations in bacteria, point mutations and gene conversion in yeast, and for cytogenetic abnormalities in rats. The results of these studies are summarized in Table VIII-3.

Henschler et al. (1977) and Taylor et al. (1977) reported that methyl chloroform was not mutagenic in the bacterial system, *Salmonella*/S9. The experimental details given in their reports were inadequate to verify the conclusions of the investigators. However, other investigators (Simmon et al. 1977 and Snow et al. 1979) independently reported that methyl chloroform was mutagenic in various *Salmonella typhimurium* strains (both with and without metabolic activation).

TABLE VIII-3 Mutagenicity Testing of Methyl Chloroform

Test System	Activation System	Result	Reference
A. Bacteria			
Salmonella/S9 (spot test and plate incorporation)	PCB induced liver, lung and testes S9	99% formulation + ive Other formulations - ive	Litton, 1975
Salmonella/S9	PCB induced rat liver microsomes S9 mix	- ive	Henschler et al. (1977)
Salmonella/S9	PCB induced rat liver microsome S9 mix	+ ive for TA 100	Simmon et al. (1977)
Salmonella/S9 (plate incorporation)	Aroclor-activated rat liver microsome S9 mix	- ive	Taylor et al. (1977)
Salmonella/S9	Methyl chloroform induced Syrian hamster liver microsome S9 mix	+ ive	Snow et al. (1979)
B. Yeast			
Saccharomyces cerevisiae (gene conversion)	PCB induced rat liver S9 mix	- ive	Litton, 1975
Schizosaccharomyces (forward mutation)	Host mediated assay B6C3F1 mice	- ive	Loprieno et al. (1979)

Methyl chloroform also was tested for mutagenic potential employing yeast as an indicator organism (Litton Bionetics 1975, Loprieno et al. 1979). The results of these tests indicated that methyl chloroform was not mutagenic in the test system *Saccharomyces cerevisiae* or *Schizosaccharomyes bombe*.

D. Quantification of Carcinogenic Effects

Using methodology described in detail elsewhere, (USEPA 1980) the EPA's Carcinogen Assessment Group (CAG, memo dated April 29, 1983) and the National Academy of Sciences (NAS 1983) have calculated estimated incremental excess cancer risks associated with exposure to methyl chloroform in drinking water, extrapolating from data obtained in the NTP repeat Bioassay in mice (NCI 1983) with this compound. CAG and NAS derived their estimates based on a statistically significant increase in hepatocellular carcinomas in mice receiving 1500 or 3000 mg/kg methyl chloroform by gavage in corn oil. The ranges of concentrations are summarized in Table VIII-4. The CAG calculated that consuming 2 liters of water per day having a methyl chloroform concentration of 2200 ug/1, 220 ug/1 or 22 ug/1 would increase the risk of one excess cancer per 10,000 (10^{-4}), 100,000 (10^{-5}) or 1,000,000 (10^{-6}) respectively, per lifetime. Similarly, the NAS also calculated excess cancer risk values based on same NCI repeat bioassay data using the multistage model. They stated that consuming 2 liters of water per day over a lifetime at a methyl chloroform

Table VIII-4 Drinking Water Concentrations and Estimated Excess Cancer Risks

Excess Lifetime Cancer Risk	Range of Concentrations (ug/l)[a]	
	CAG[b]	NAS[c]
10^{-4}	2200	1680
10^{-5}	220	168
10^{-6}	22	16.8
0	0.00	0.00

[a] Assumes the consumption of two liters of water per day by 70 kg adult over a lifetime; number represents 95% upper bound confidence limit

[b] (McGaughy 1983)

[c] (NAS 1983)

concentration of 1680 ug/1, 168 ug/1 or 16.8 ug/1 would increase the risk of one excess cancer per 10,000 (10^{-4}), 100,000 (10^{-5}), or 1,000,000 (10^{-6}) people exposed, respectively. The slight difference between CAG and NAS values is due to the fact that CAG has taken into consideration hepatocellular carcinomas observed in the female mice whereas the NAS have included in the derivation of risk values the results of both male and female mice hepatocellular carcinomas.

In the quantification of toxicological effects for a chemical, consideration should be given to subgroups within the general population which are at greater than average risk upon exposure to the chemical. For methyl chloroform, animal studies have not been carried out to characterize adverse effects in the aged or newborn.

Methyl chloroform has also been shown to have interaction with other chemicals. Ingestion of ethanol was shown to increase the hepatotoxicity of methyl chloroform. However, ingestion of isopropyl alcohol or acetone prior to administration of methyl chloroform did not alter the response of enzyme activity.

The latest bioassay data on 1,1,1-trichloroethane is currently undergoing audit by NTP and a final report has not been issued. Therefore, this proposal will use the non cancer inhalation data as the basis for the proposed RMCL. This approach will be amended if the final NTP report determines that 1,1,1-trichloroethane was carcinogenic under the condition of the text.

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